THE LANCET
Healthy Longevity

## Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Hudson J, Cruickshank M, Quinton R, et al. Adverse cardiovascular events and mortality in men during testosterone treatment: an individual patient and aggregate data meta-analysis. *Lancet Healthy Longev* 2022; **3:** e381–93

## Ovid (Medline and Embase) search strategy

Database: Ovid Embase <1980 to 2018 Week 35>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to August 24, 2018>

Date of search 27th August 2018

1 exp androgens/tu use ppez (7642)
2 hormone replacement therapy/ use ppez (9272)
3 2 and (men or androgen? or testosterone).af. (2597)
4 Androgen Therapy/ use emez (5220)
5 (androgen replacement therapy or art).tw,kw. (186233)
6 testosterone.tw,kw. (161015)
7 or/1,3-6 (353317)
8 exp Erectile Dysfunction/ use ppez (17850)
9 exp impotence/ use emez (38953)
10 Sexual Dysfunction, Physiological/ (22063)
11 testosterone/df (1227)
12 Libido/ use ppez (4538)
13 Libido Disorder/ use emez (5704)
14 Hypogonadism/ (21649)
15 (erectile adj3 dysfunction).tw,kw. (37580)
16 (libido adj3 (low$ or decreas$ or reduc$ or loss)).tw,kw. (4553)
17 (impotence or impotent).tw,kw. (14427)
18 hypogonad$.tw,kw. (28070)
19 (low$ adj3 testosterone).tw. (11853)
20 (deficien$ adj3 (androgen or gonad$ or testosterone)).tw. (8153)
21 (insuffic$ adj3 (androgen or gonad$ or testosterone)).tw. (953)
22 (kallman or klinefetter).tw. (181)
23 or/8-22 (140217)
24 7 and 23 (30320)
25 exp clinical trial/ use emez (1309842)
26 randomized controlled trial.pt. (467661)
27 controlled clinical trial.pt. (92614)
28 randomization/ use emez (78791)
29 randomi?ed.ab. (1210469)
30 placebo.ab. (452150)
31 drug therapy.fs. (5417963)

32 randomly.ab. (676570)
33 trial.ab. (1049510)
34 groups.ab. (4245410)
35 or/25-34 (10765717)
36 exp animals/ not humans/ (15654408)
37 nonhuman/ not human/ (4188739)
38 35 not (36 or 37) (7089138)
39 24 and 38 (9708)
40 limit 39 to english language (8722)
41 limit 40 to (english language and yr="1992 -Current") (7714)
42 41 not ((women not men) or (female not male)).tw. (6951)
43 41 and male/ (5690)
44 42 or 43 (7041)

## Secondary outcomes

- Quality of Life
    - SF-36/SF-12
    - Aging Males Symptoms (AMS)
    - WHOLQOL-OLD
    - Herschbach-questionnaire
- Sexual function
    - The International Index of Erectile Function – 15 (IIEF-15)
    - The International Index of Erectile Function – 5 (IIEF-5)
    - Androgen Deficiency in the Aging Men (ADAM)
    - Psychosexual Daily Questionnaire (PDQ)
    - Derogatis Interview for Sexual Functioning in Men-II5 (DISF-II)
    - Eleven question about Sexual Functioning (ESF)
    - Hypogonadism Energy Diary (HED)
    - Sexual Arousal, Interest, and Drive Scale (SAID)
    - Male Sexual Health Questionnaire-Ejaculatory Dysfunction-Short Form (MSHQ)
- Physiological Markers
    - Testosterone (nmol/L)
    - Free testosterone (pmol/L)
    - Fasting Glucose (mmol/L)
    - Cholesterol (mmol/L)
    - LDL (mmol/L)
    - HDL (mmol/L)
    - Triglycerides (mmol/L)
    - Haemoglobin (g/L)
    - HbA1c (mmol/mol)
    - Haematocrit (%)
    - SBP (mmHg)
    - DBP (mmHg)
    - Areal bone mineral density (BMD)
    - Volumetric bone mineral density
- Psychological symptoms
    - Beck Depression Inventory (BDI)
    - Positive and Negative Affect Scale (PANAS)
    - Hospital Anxiety and Depression Scale (Depression only) HADS-Depression
    - Patient Health Questionnaire-9 (PHQ-9)
    - Centre for Epidemiologic Studies Depression Scale (CES-D)
    - Aggression questionnaire
    - Speilberger State-Trait Anxiety
    - The Geriatric Depression Scale (GDS)
    - Hamilton Depression and Melancholia Scale
    - Profile of Mood States (POMS)

## Additional outcomes

- Diabetes/diabetes complications
- Prostate cancer
- Oedema
- Hypertension
- High Haematocrit
- Venous thromboembolism
- Non-stroke cerebrovascular pathology (e.g. carotid occlusion and carotid stenosis).

# Testosterone Effects and Safety in Men with Low Testosterone levels (TESTES): An evidence synthesis and economic evaluation

## NIHR HTA Programme (project no. 17/68/01)

## Statistical analysis plan

Version Number: V1

| | | |
|---|---|---|
| Senior Statistician<br>Lorna Aucott | Signature | Date |
| Principal Investigator<br>Channa Jayasena | Signature | Date |
| Author<br>Jemma Hudson | Signature | Date |

# Contents

# 1. Amendment history

This is the first version of the TESTES statistical analysis plan (SAP).

# 2. Abbreviations (to be finalised once complete)

| Abbreviation | Definition |
|---|---|
| AMS | Aging Males' Symptoms |
| ART | Androgen replacement therapy |
| BDI | Beck Depression Inventory |
| ESS | Epworth Sleepiness Scale |
| EQA | External quality control |
| HADS | Hospital Anxiety & Depression Score |
| IPD | Individual Participant Data |
| ITT | Intention-to-treat |
| IQA | Internal quality control |
| IIEF | International Index of Erectile Function |
| PROMs | Patient reported outcome measures |
| SAP | Statistical analysis plan |
| TESTES | Testosterone Effects and Safety in Men with Low Testosterone levels |

# 3. Introduction

As part of the Testosterone Effects and Safety in Men with Low Testosterone Levels (TESTES) study an Individual Patient Data (IPD) meta-analysis will be performed to identify, for the first time, which specific patient groups may benefit most from androgen replacement therapy (ART), and which may be at risk of experiencing harmful effects.

The Statistical Analysis Plan (SAP) for the TESTES IPD meta-analysis is detailed below. This SAP should be read alongside the research protocol (PROSPERO registration no CRD42018111005).

## 3.1. Aims and objectives of the TESTES project

To determine the clinical effectiveness, safety, cost-effectiveness and acceptability of ART in symptomatic men with testosterone deficiency.

Specific objectives are as follows:

i) To conduct a comprehensive systematic review and IPD meta-analysis to estimate the clinical effectiveness and safety of ART for men with testosterone deficiency syndrome and to provide the key parameters for the development of a decision model;
ii) To conduct a systematic review of existing qualitative evidence, which reports men's experience and acceptability of ART, and an analysis of patient reported outcome measures (PROMs);
iii) To develop a decision model to estimate the cost-effectiveness of ART for the treatment of symptomatic men with low testosterone.

This statistical analysis plan will only focus on point (i) of the objectives.

## 3.2. Outcomes

Relevant outcomes will be collected at 12 months or the nearest time point to 12 months.

### 3.2.1. Primary outcomes

- Mortality from any cause during the study period.
- Combination of Cardiovascular and/or cerebrovascular events (e.g., fatal and non-fatal myocardial infarction, angioplasty, coronary artery bypass, arrhythmias, peripheral oedema, elevated blood pressure, acute coronary syndrome, fatal and non-fatal stroke, and transient ischaemic attack).

### 3.2.2. Secondary outcomes

- Quality of life measured through validated scores, whether generic and/or disease-specific (e.g., EuroQoL - EQ-5D, Hospital Anxiety & Depression Score - HADS, Beck Depression Inventory - BDI, Epworth Sleepiness Scale - ESS, Aging Males' Symptoms – AMS)
- Sexual function and symptoms (e.g., self-reported early morning erections, ability to maintain erection during intercourse, frequency of intercourse). Where possible, these will be quantified by validated scores such as, but not limited to, the International Index of Erectile Function (IIEF).
- Physiological markers (e.g., blood pressure, haemoglobin concentration, haematocrit; total serum lipid profile, plasma glucose, bone mineral density, obstructive sleep apnoea).
- Psychological symptoms (e.g., cognition, mood and behaviour assessed by validated scores).
- Diagnosis of prostate cancer
- Diabetes/diabetes complications

## 4. Data collection

Investigators of trials who have agreed to collaborate to the TESTES project will be asked to complete a key items form (see Appendix 1). IPD requested include primary and secondary outcomes as well as the following:

- Study level data
    - Number randomised to the ART group
    - Number randomised to the placebo/standard care group

- Baseline characteristics (individual participant data)
    - Patient ID
    - Centre ID
    - Demographics:
    - Medical history:

The original study protocol alongside with any case report form and/or questionnaire will be sought from the TESTES trials' investigators.

## 5. Data checking and standardisation

Once the IPD data have been obtained, we will produce summary statistics to ensure that the data match those given in the published output of the trials. If there are any discrepancies, we will

communicate with the collaborators to solve these. We will also standardise outcomes on a common scale using the appropriate conversions.

# 6. Statistical analysis

The main statistical analysis will be conducted according to the intention-to-treat (ITT) principle. All outcomes will be analysed in a similar way apart from diagnosis of prostate cancer and diabetes/diabetes complications which will be summarised descriptively.

## 6.1. Descriptive analysis

Baseline characteristics and outcome measures will be described by randomised group using appropriate summary statistics and graphical presentations. For the primary outcomes, mortality and combination of cardiovascular and/or cerebrovascular events, we will report a breakdown of the individual events e.g. number of myocardial infarction events

## 6.2. IPD meta-analysis

We will perform IPD meta-analyses for the pre-specified outcome measures from all eligible trials. The IPD approach will allow us to investigate whether the observed effects of ART are consistent across participants with certain characteristics.

A feature of the IPD approach is to preserve the clustering of participants within trials. Two methods are currently recommended: the two-step approach and the one-step approach. The one-step approach permits modelling of IPD from all trials simultaneously while stratifying or accounting for differences between trials; it may be more appropriate for non-normal outcomes and when studies are small, events rare and/or when an effect is large. Nevertheless, it can be computationally intensive and prone to convergence problems and assumes that IPD for all randomised trials can be obtained. In the two-step approach, aggregate data for each trial are synthesised using standard meta-analysis methods for aggregate data (e.g., assuming fixed or random effects across trials). Meta-analyses results are displayed on forest plots. The two approaches often produce similar results especially if the study estimates are approximately normally distributed with known variances. Our preferred approach is the one-step IPD meta-analysis, however, if need be, we will also perform the two-step approach.

The analyses will use multilevel regression models suitable for the outcome data type with adjustment for baseline values, if appropriate. A random effects approach to the intervention effect will be preferred over a fixed effects approach; however, when the between studies standard deviation is very low, fixed effects one-stage models will be considered to avoid or reduce failure of model convergence.

Counter-enhanced funnel plots and tests for asymmetry will be considered for assessing small-study effects and publication biases, respectively.

If it is not possible to retrieve an acceptable amount of individual participant data, we will perform a standard meta-analysis of aggregated data.

## 6.3. Standard meta-analysis

In addition to the IPD analysis a standard meta-analysis of the aggregated data will be conducted [according to standard Cochrane methodology (ref: Cochrane Handbook)].

## 6.4. Missing data

For the IPD analysis, a complete data analysis will be performed when participants' data are missing. In the presence of substantial missing data (10% for any relevant outcome or covariate), sensitivity analyses will be considered to assess the impact of missing data which may include multiple imputation or pattern mixture models. A further sensitivity analysis will look at the effect of any heterogeneous studies e.g. by excluding these from the analysis.

## 6.5. Subgroup analysis

IPD will permit categorisation of participants for subgroup analyses defined according to specific modification factors. If possible, subgroup analyses will be used to explore the potential effects of baseline testosterone levels (<8, 8-10, 10-12, >12nmol/L), free (calculated or measured) serum testosterone levels (<180, 180-220, >220pmol/L), diabetes and smoking status on the primary outcomes. Subgroup by treatment interactions will be assessed by including interaction terms in the model.

# 7. Appendix

***NIHR TESTES - List of core items***

**We would be grateful if you could complete this form to tell us what type of data you hold. Also, can you please send the protocol and any examples of case report forms and questionnaires.**

**Ideally, we would like to receive the data in the format specified below. However, we will accept them in any coding system and in any suitable format along with a data dictionary.**

**Data format: Stata**

| Type of data | |
|---|---|
| **Study level data** | Geographical location (country or countries) in which the trial was carried out) |
| | Number of trial centres (e.g. a single centre trial =1; a multi-centre trial will be >1) |
| | Number randomised to the ART group |
| | Number randomised to the placebo/standard care group |
| | Setting (primary care, hospital, community) |
| | Date first patient randomised |
| | Date final patient randomised |
| | Date of final patient follow-up |
| | Inclusion criteria: Testosterone (total and / or free) threshold |
| | Inclusion criteria: all others |
| | Exclusion criteria: |
| | Testosterone assay methodology including internal quality control (IQA) and / or external quality control (EQA). IQA/ EQA are surveillance systems to ensure assay alignment e.g. comparison of standard sample between operators [IQA] or labs[EQA]. |

| Type of data | |
|---|---|
| | Evidence of testosterone assay performance against Mass Spectrometry (Immunoassay only) |
| | Details of ART during the protocol (product, dosing regimen, duration of treatment, etc.) |
| | Details of comparator (dose, duration of treatment, etc.) |
| | Did the study measure quality of life (state tool that was used e.g., questionnaire, interview)? |
| **Individual participant data** | **Baseline characteristics** |
| *Patient ID* | |
| *Centre ID* | |
| *Demography* | Age (unit) |
| | Weight (unit) |
| | Height (unit) |
| | Ethnic group |
| | Date of entry into study/date of randomisation |
| | Allocated to ART or placebo |
| *Medical history* | |

| Type of data | |
|---|---|
| | Previous myocardial infarction or angina |
| | Previous stroke |
| | History or family history of prostate cancer |
| | Glucose, HbA1c or diagnosis of diabetes mellitus (date of diagnosis, any treatment for diabetes) |
| | History of atrial fibrillation |
| | History of coronary artery disease or bypass graft surgery |
| | History of hypertension |
| | History of heart failure |
| | Evidence of atherosclerosis |
| | Any other cardiac co-morbidity |
| | Lipid measurements or treatment / diagnosis of hyperlipidaemia |
| | Sexual symptoms (e.g. spontaneous erections, diagnosis of erectile dysfunction, libido) |
| | Physical parameters (e.g., muscle mass and strength, exercise tolerance, body weight, body mass index, total lean body mass, fat mass). |
| | Fatigue (please specify any validated score if used) |

| Type of data | |
|---|---|
| | Mood symptoms e.g. low mood, depression, anxiety (please specify any validated score if used) |
| | Sleep disturbances |
| | Cognitive impairment e.g. memory loss, dementia (please specify any validated score if used) |
| | History of anaemia |
| | History of osteoporosis or fracture |
| | History of frailty or falls |
| | Other - Please include any other baseline characteristics not mentioned |
| **Individual Participant Data** | **Outcomes** |
| | Randomised to control or ART? |
| | Mortality and cause of mortality |
| | Sexual function (measured by the International Index of Erectile Function – IIEF or other validated tools) |
| | Prostate-related outcomes (e.g., prostate-specific antigen levels, prostate volume, increase in the International Prostate Symptoms Score) |

| Type of data | |
|---|---|
| | Cardiac outcomes (e.g., cardiovascular and cerebrovascular events -such as myocardial infarction, angioplasty, coronary artery bypass, arrhythmias, peripheral oedema, elevated blood pressure, stroke; incidence of diabetes) |
| | Other adverse outcomes: Diagnosis of diabetes, hyperlipidaemia, osteopenia / osteoporosis |
| | Physiological markers (e.g., blood pressure, haemoglobin concentration, haematocrit; total serum lipid profile, plasma glucose or HbA1c, bone mineral density) |
| | Sexual symptoms (e.g., spontaneous erections, diagnosis of erectile dysfunction, libido) |
| | Physical parameters (e.g., muscle mass and strength, exercise tolerance, body weight, body mass index, total lean body mass, fat mass). |
| | Psychological symptoms (e.g., cognition by validated score) |
| | Mood outcomes (e.g., diagnosis of depression, psychiatric illness, mood scores) |
| | Functional activities (e.g., running, walking, kneeling; quantified where possible by validated scores such as the SF-36) |
| | Quality of life (e.g. EuroQoL - EQ-5D, Hospital Anxiety & Depression Score - HADS, Beck Depression Inventory - BDI, Epworth Sleepiness Scale ESS, Aging Males' Symptoms - AMS) |
| | Other |
| **Drop-outs** | |
| | Date of study discontinuation |

| Type of data | |
|---|---|
| | Reason for study discontinuation |

## Study characteristics

**Table 1. Summary of the characteristics of the 17 studies, which provided IPD**

| Study ID (geographical location) | Study design | No of centres | Total n randomised | Study duration | Study dates | Testosterone assay as reported by the study authors | Details of intervention |
|---|---|---|---|---|---|---|---|
| Amory 2004[1] (USA) | RCT Phase NR | 1 | 48 | 3 years[1] | June 1993 to June 1995 | Fluoroimmunoassay (Delfia, Wallac Oy, Turku, Finland) | Testosterone injection 200mg every 2 weeks |
| Basaria 2010[2] (USA) | RCT Phase 4 | 3 | 209 | 6 months | September 2005 to December 2009 | Immunoassay (Quest) | Testosterone gel, 10g (100mg testosterone) once daily |
| Basaria 2015[3] (USA) | RCT Phase 4 | 3 | 308 | 3 years[2] | September 2004 to February 2009 | Bayer Advia Centaur immunoassay (Siemens Healthcare Diagnostics) | Testosterone gel, 7·5g of 1% testosterone gel daily |
| Brock 2016[4] (Argentina, Canada, Germany, Spain, Italy, South Korea, Puerto Rico, UK, USA) | RCT Phase 3 | 98 | 715 | 12 weeks | NR | Liquid chromatography-mass spectrometry/mass spectrometry | Testosterone gel, 60mg testosterone 2% once daily |

| Study ID (geographical location) | Study design | No of centres | Total n randomised | Study duration | Study dates | Testosterone assay as reported by the study authors | Details of intervention |
|---|---|---|---|---|---|---|---|
| Emmelot-Vonk 2008[5] (Netherlands) | RCT Phase 2/3 | 1 | 237 | 6 months | January 2004 to April 2005 | Solid phase, competitive, chemiluminescent enzyme immunoassay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, California) | Testosterone capsules, two 40mg capsules twice daily |
| Gianatti 2014a[6] (Australia) | RCT Phase 2/3 | 1 | 88 | 40 weeks | November 2009 to February 2013 | Electrochemiluminescence Immunoassay (ECLIA) and liquid chromatography-tandem mass spectroscopy (LCMS/MS) | Testosterone injection, 1000mg at weeks 0, 6, 18 and 30 |
| Giltay 2010a[7] (Russia) | RCT Phase 3 | 1 | 184 | 30 weeks | October 2005 to October 2008 | Vitros 3600 system (Ortho-Clinical Diagnostics, Johnson & Johnson company, New Brunswick, NJ, SA) with a chemiluminescence immunoassay technology | Testosterone injection, 1000mg at weeks 0, 6 and 18 |
| Groti 2018[8] (Slovenia) | RCT Phase NR | 1 | 55 | 12 months | January 2014 to March 2018 | Immulite 2000 chemiluminescent enzyme immunoassay (Siemens Healthcare GmbH) | Testosterone injection, 1000mg at weeks 0, 5 and then 10-week intervals |
| Hackett 2013[9] (UK) | RCT Phase NR | 8 | 199 | 30 weeks | September 2008 to June 2011 | Roche common platform immunoassay | Testosterone injection, 1000mg at weeks 0, 6 and 18 |

| Study ID (geographical location) | Study design | No of centres | Total n randomised | Study duration | Study dates | Testosterone assay as reported by the study authors | Details of intervention |
|---|---|---|---|---|---|---|---|
| Hildreth 2013[10] (USA) | RCT Phase NR | 1 | 83 | 12 months | January 2005 to March 2009 | ELISA using a Beckman Coulter (Brea, California) Access II analyzer | Testosterone gel, 5g to 10g daily |
| Ho 2012[11] (Malaysia) | RCT Phase NR | 1 | 120 | 48 weeks | May 2008 to February 2010 | Immunoassay using a AxSYM testosterone assay (Abbott Laboratories, Wiesbaden, Germany), based on microparticle enzyme immunoassay technology | Testosterone injection, 1000mg at weeks 0, 6, 18, 30 and 42 |
| Magnussen 2016[12] (Denmark) | RCT Phase 4 | 1 | 43 | 24 weeks | April 2012 to November 2013 | Liquid chromatography tandem mass spectrometry after ether extraction (Statens Serum Institut, Copenhagen, Denmark) | Testosterone gel, 5g daily |
| Marks 2006[13] (USA) | RCT Phase 2/3 | 1 | 44 | 6 months | February 2003 to November 2004 | Mass spectroscopy | Testosterone gel, 150mg biweekly |
| Merza 2006[14] (UK) | RCT Phase NR | 1 | 39 | 6 months | NR | IRMA (Orion Diagnostics) | Testosterone patch, delivering 5mg/day |
| Snyder 2016[15] (USA) | RCT Phase 3 | 12 | 790 | 12 months | June 2010 to June 2013 | Liquid chromatography with tandem mass spectroscopy | Testosterone gel, 5g daily |

| Study ID (geographical location) | Study design | No of centres | Total n randomised | Study duration | Study dates | Testosterone assay as reported by the study authors | Details of intervention |
|---|---|---|---|---|---|---|---|
| Srinivas-Shankar 2010[16] (UK) | RCT Phase NR | 1 | 274 | 6 months | NR | Chemiluminescent immunoassay with a Roche Elecys E170 platform | Testosterone gel, 50mg daily |
| Svartberg 2008[17] (Norway) | RCT Phase NR | 1 | 38 | 12 months | 2005 | Electrochemical luminescence immunoassay using an automated clinical chemistry analyser (Modular E; Roche Diagnostics GmbH, Mannheim, Germany) | Testosterone injection, 1000mg at weeks 0, 6, 16, 28, 40 |

**Notes.** ELISA: enzyme-linked immunosorbent assay, IRMA: immunoradiometric assay, RIA: radioimmunoassay, NR: not reported. Manufacturer of testosterone assay method was not reported for all studies. [1]Outcome data was used at 12 months. [2]Secondry outcome data was used at 18 months and primary outcome data was at 3 years due to being unable to confirm the time frame these events occurred.

**Table 2. Summary of the characteristics of the 18 studies, which did not provide IPD**

| Study ID (geographical location) | Study design | No of centres | Total n randomised | Study duration | Study dates | Testosterone assay as reported by the study authors | Details of intervention |
|---|---|---|---|---|---|---|---|
| Aversa 2010a[18] (Italy) | RCT Phase NR | 1 | 50 | 12 months | NR | Electrochemiluminescence (Immulite 2000 Siemens, Milan, Italy) | Testosterone injection, 1000mg every 12 weeks from week 6 |
| Aversa 2010b[19] (Italy) | RCT Phase NR | NR | 52 | 12 months | NR | Electrochemiluminescence (Immulite 2000 Siemens, Milan, Italy) | Testosterone capsules, two 40mg capsules twice daily; Testosterone injection, 1000mg every 12 weeks from week 6 |
| Basurto 2008[20] (Mexico) | RCT Phase NR | 1 | 48 | 12 months | November 2002 to January 2005 | Specific solid-phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA) | Testosterone injection, 250mg every 21 days |
| Behre 2012[21] (Austria, Finland, Germany, Ireland, Italy, Spain, Sweden, UK) | RCT Phase NR | NR | 362 | 6 months | NR | Electrochemiluminescence immunoassay technique on a Roche Elecsys or Modular E170 analyzer | Testosterone gel, 5g testosterone 1% gel daily |
| Borst 2014[22] (USA) | RCT Phase 2 | NR | 30 | 12 months | NR | Electrochemiluminescence immunoassay (Cobas) | Testosterone injection, 125mg weekly |

| Study ID (geographical location) | Study design | No of centres | Total n randomised | Study duration | Study dates | Testosterone assay as reported by the study authors | Details of intervention |
|---|---|---|---|---|---|---|---|
| Cavallini 2004[23] (Italy) | RCT Phase 2 | NR | 85 | 6 months | January 2002 to June 2002 | Recombinant immunoassay after extraction and celite chromatography (Diagnostic Products, Los Angeles, CA) | Testosterone tablets, 160mg daily |
| Cherrier 2015[24] (USA) | RCT Phase NR | 1 | 22 | 6 months | NR | Liquid chromatography tandem mass spectrometry | Testosterone gel, 50mg to 100mg daily |
| Chiang 2007[25] (Taiwan) | RCT Phase NR | 2 | 40 | 3 months | November 2002 to November 2004 | Radioimmunoassay | Testosterone gel, 50mg daily |
| Clague 1999[26] (UK) | RCT Phase NR | 1 | 14 | 12 weeks | NR | NR | Testosterone injection, 200mg every two weeks |
| Dhindsa 2016a[27] (USA) | RCT Phase 4 | 1 | 44 | 22 weeks | December 2010 to January 2014 | Liquid chromatography–tandem mass spectrometry (Quest Diagnostics) | Testosterone injection, 250mg every two weeks |
| Dias 2016[28] (USA) | RCT Phase 2 | 1 | 29 | 12 months | March 2004 to December 2013 | Liquid chromatography tandem mass spectroscopy | Testosterone gel, 5g daily |
| Jones 2011[29] (Belgium, France, Germany, Italy, | RCT Phase NR | 36 | 220 | 12 months | February 2006 to March 2007 | NR | Testosterone gel, 3g testosterone 2% daily |

| Study ID (geographical location) | Study design | No of centres | Total n randomised | Study duration | Study dates | Testosterone assay as reported by the study authors | Details of intervention |
|---|---|---|---|---|---|---|---|
| Netherlands, Spain, Sweden, UK) | | | | | | | |
| Kaufman 2011a[30] (USA) | RCT Phase 3 | 63 | 274 | 182 days | February 2007 to April 2007 | Liquid chromatography/tandem mass spectrometry (Pharmaceutical Product Development, Richmond, VA) | Testosterone gel, 2·5g to 5g testosterone 1.62% gel daily |
| Kenny 2010[31] (USA) | RCT Phase 4 | 1 | 131 | 12 months | NR | Radioimmunoassay (Endocrine Sciences Inc, Calabasas Hills, CA) | Testosterone gel, 5mg testosterone 1% gel daily |
| Morales 2009[32] (Canada) | RCT Phase 2 | 4 | 58 | 4 months | NR | NR | Testosterone capsules, 80mg twice daily |
| Paduch 2015a[33] (USA,Canada, Mexico) | RCT Phase NR | NR | 76 | 16 weeks | August 2011 to December 2013 | Liquid chromatography tandem mass spectrometry | Testosterone gel, 60mg testosterone 2% gel daily |
| Steidle 2003[34] (USA) | RCT Phase NR | 43 | 406 | 90 days | NR | Radioimmunoassay (Diagnostic Products, Los Angeles, CA) | Testosterone gel, 50mg or 100mg daily |
| Wang 2013[35] (China) | RCT Phase NR | 1 | 186 | 24 months | NR | Chemical luminescence | Testosterone capsules, 20mg or 40mg daily |

**Notes.** NR: not reported. Manufacturer of testosterone assay method was not reported for all studies

## Baseline characteristics continued

**Table 1. Baseline characteristics of the participants enrolled in the 17 studies that contributed to the IPD**

| Baseline characteristic | Number of studies | TRT N=1750 | Placebo N=1681 |
|---|---|---|---|
| Areal bone mineral density (g/cm2) | | | |
| Total | 4 | 1·21 (0·14); 416 | 1·21 (0·12); 380 |
| Sub-total | 2 | 1·03 (0·10); 126 | 1·02 (0·09); 120 |
| Femoral neck | 6 | 0·84 (0·14); 270 | 0·86 (0·16); 231 |
| Lumbar spine | 10 | 1·17 (0·21); 550 | 1·17 (0·23); 512 |
| Thoracic spine | 2 | 0·95 (0·15); 180 | 0·91 (0·14); 157 |
| Total hip | 9 | 1·02 (0·14); 420 | 1·03 (0·15); 380 |
| Trochanter | 3 | 0·78 (0·12); 97 | 0·76 (0·11); 70 |
| Intertrochanter | 2 | 1·15 (0·16); 37 | 1·16 (0·16); 37 |
| Pelvis | 2 | 1·23 (0·19); 175 | 1·20 (0·16); 140 |
| Left arm | 3 | 0·85 (0·11); 202 | 0·83 (0·07); 176 |
| Right arm | 3 | 0·86 (0·12); 202 | 0·84 (0·08); 177 |
| Left plus right arm | 1 | 1·63 (0·12); 20 | 1·57 (0·40); 19 |
| Left leg | 3 | 1·26 (0·17); 192 | 1·23 (0·11); 159 |
| Right leg | 3 | 1·26 (0·15); 188 | 1·26 (0·18); 154 |
| Left plus right leg | 1 | 2·42 (0·22); 20 | 2·30 (0·63); 18 |
| Left rib | 2 | 0·71 (0·08); 179 | 0·69 (0·07); 155 |
| Right rib | 2 | 0·72 (0·08); 182 | 0·69 (0·07); 159 |
| Head | 2 | 2·11 (0·30); 183 | 2·06 (0·33); 159 |
| Shaft | 1 | 1·21 (0·17); 54 | 1·17 (0·15); 28 |
| Wards | 1 | 0·60 (0·16); 54 | 0·54 (0·12); 28 |
| Volumetric bone mineral density (mg/cm3) | 1 | | |
| Spine trabecular | | 102·39 (31·91); 110 | 99·37 (26·95); 97 |
| Spine cortical | | 285·40 (42·47); 110 | 284·18 (43·31); 97 |
| Spine whole | | 193·35 (37·24); 110 | 192·64 (34·90); 97 |
| Hips trabecular | | 185·42 (34·32); 103 | 180·72 (33·05); 88 |
| Hips cortical | | 398·99 (46·36); 103 | 391·68 (50·22); 88 |
| Hips whole | | 248·78 (37·86); 103 | 243·06 (38·86); 88 |

Values are mean (standard deviation); numbers or numbers (percent).

## Risk of Bias

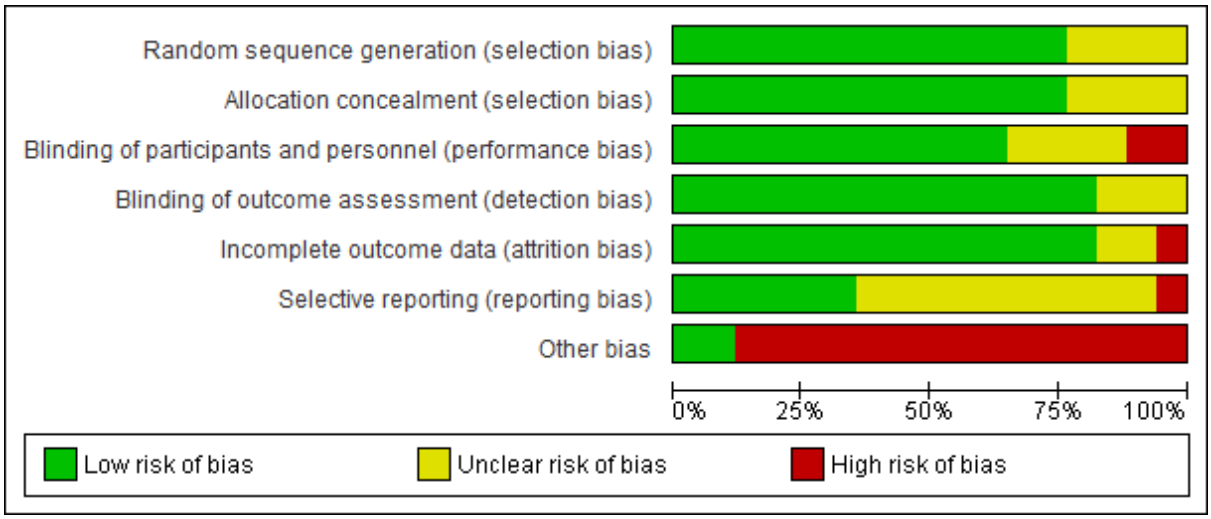



**Figure 1. Summary of the risk of bias assessment of the 17 IPD studies (data derived from published reports and from contacting the collaborators)**

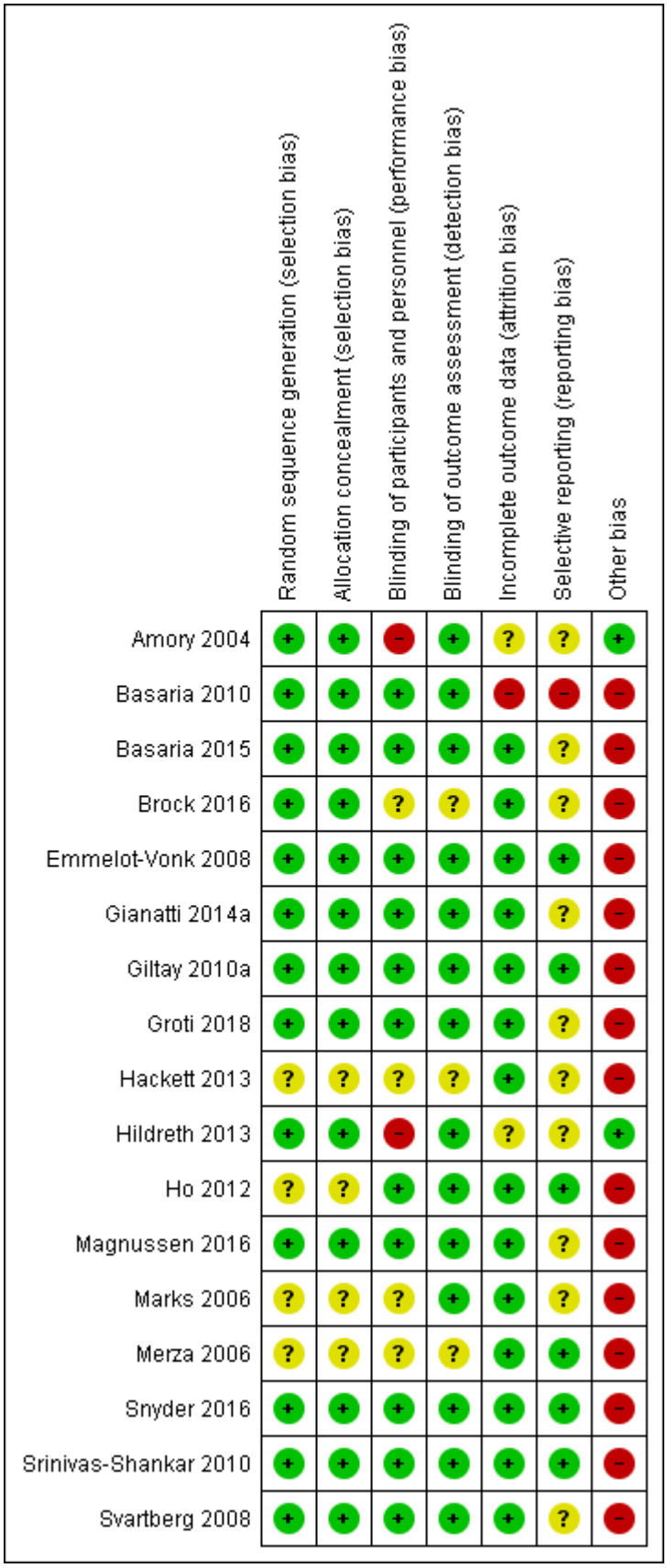



**Figure 2. Risk of bias assessments of the 17 IPD studies (data derived from published reports and from contacting the collaborators)**

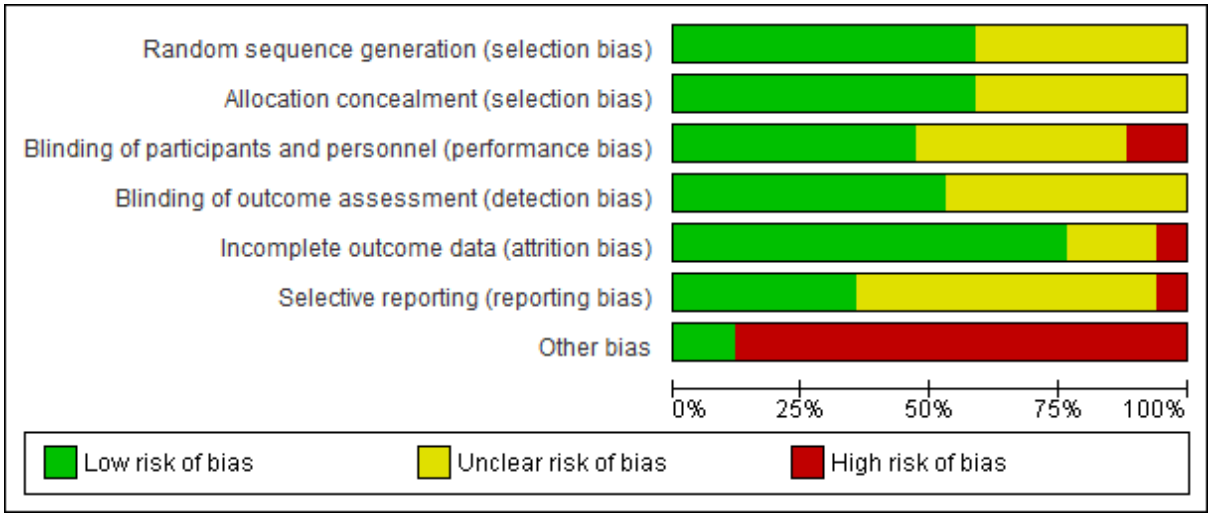



**Figure 3. Summary of the risk of bias assessment of the 17 IPD studies (data from published reports only)**

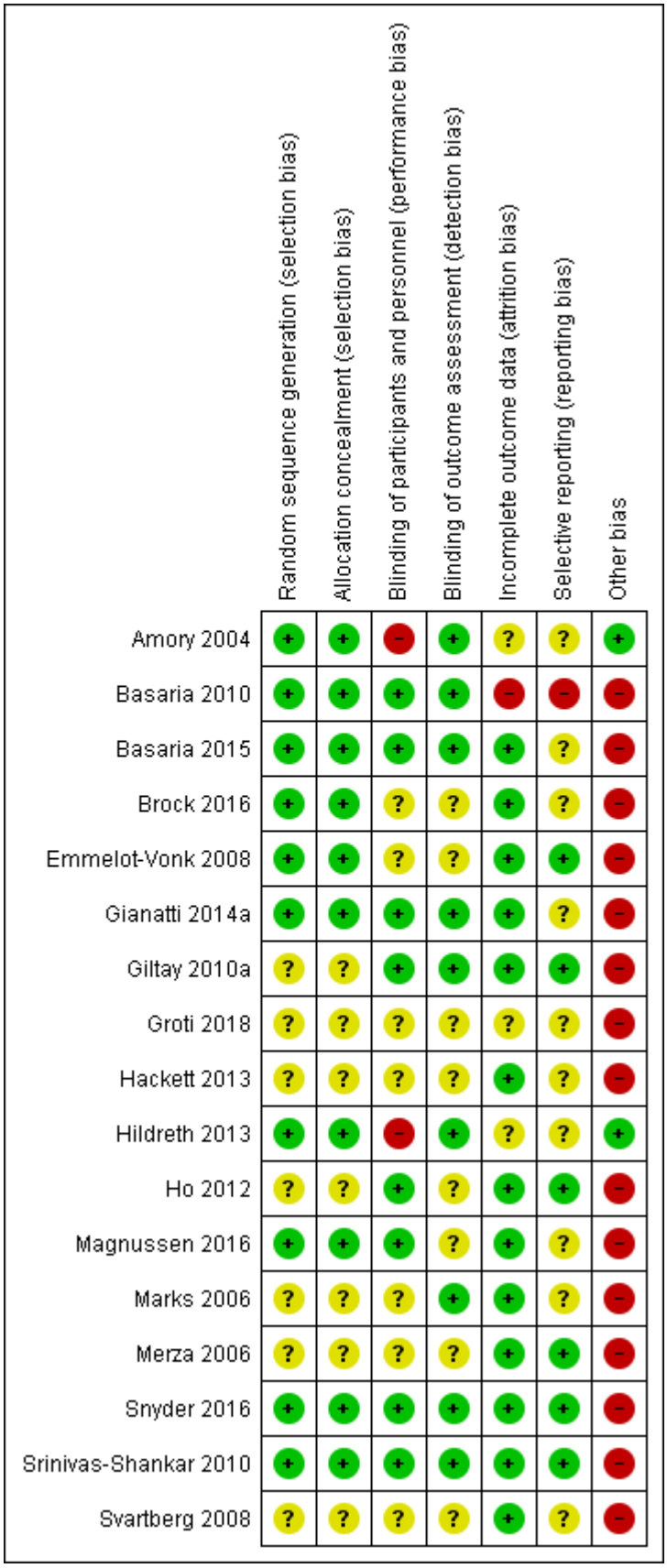



**Figure 4. Risk of bias assessments of the 17 IPD studies (data from publications only)**

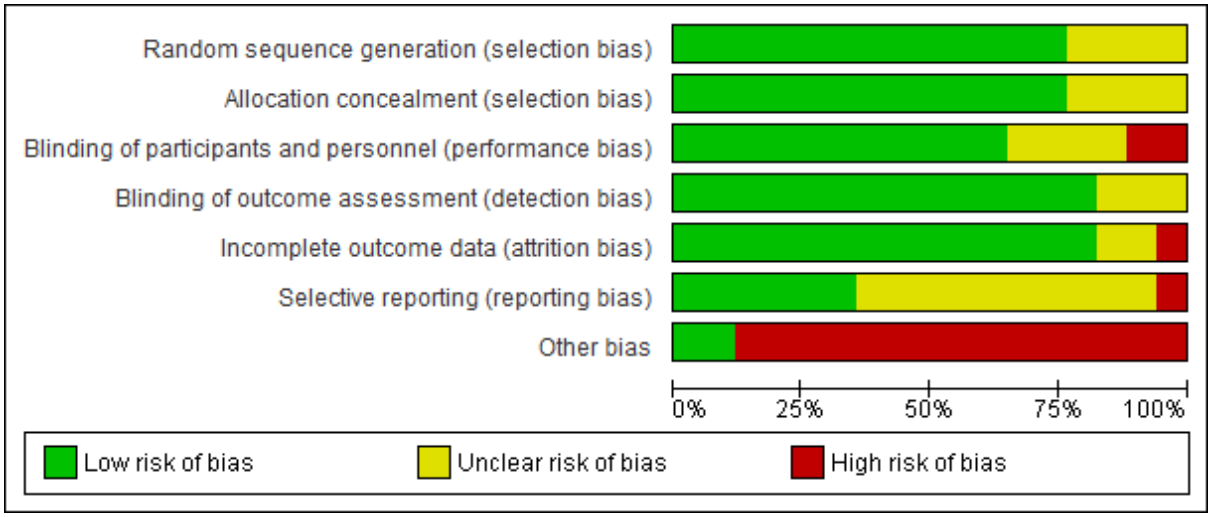



**Figure 5. Summary of the risk of bias assessment of the 17 IPD studies (data derived from published reports and from contacting the collaborators)**

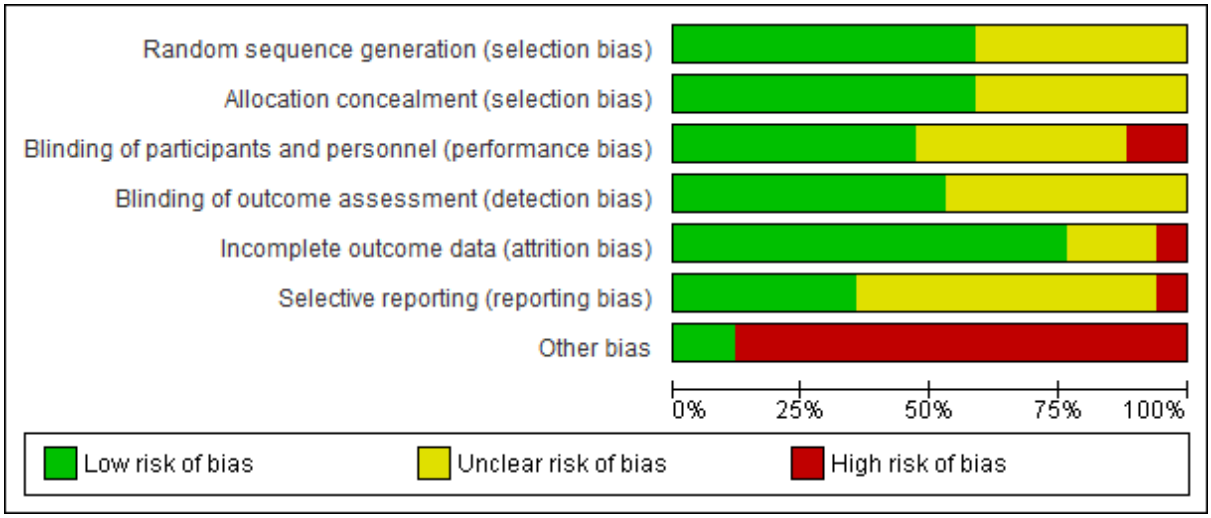



**Figure 6. Summary of the risk of bias assessment of the 17 IPD studies (data from published reports only)**

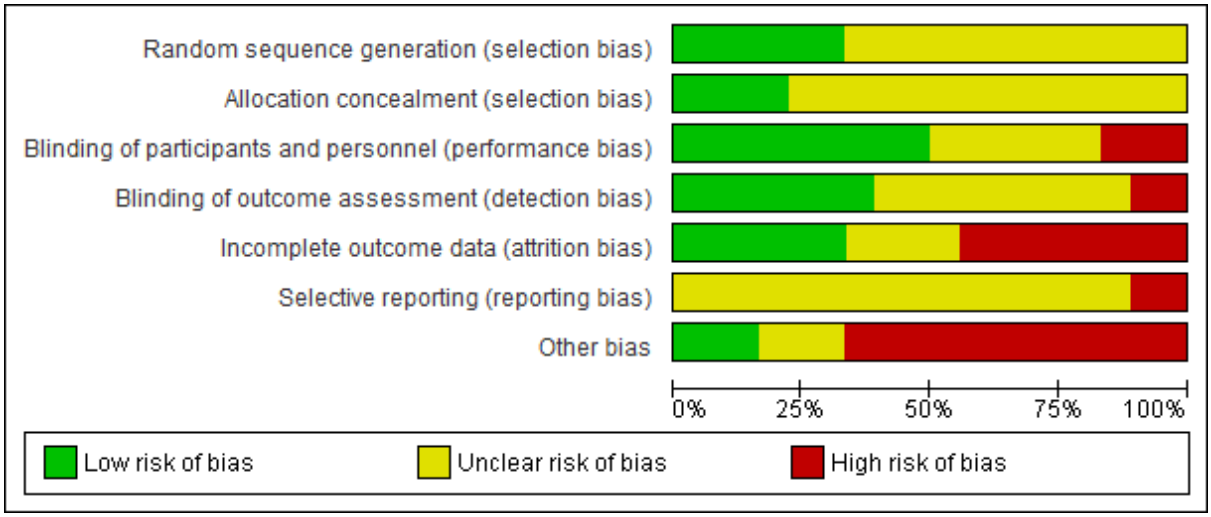



**Figure 7. Summary of risk of bias assessment of the 18 non-IPD studies**

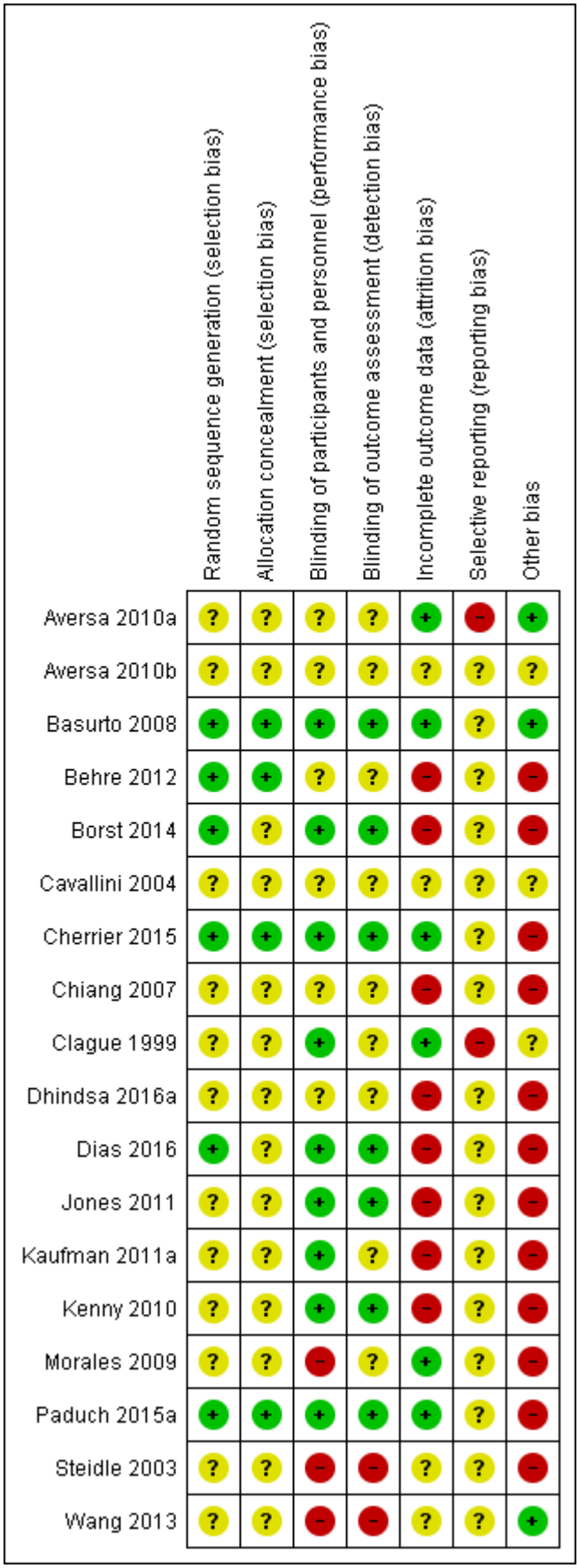



**Figure 8. Risk of bias assessments of the 18 non-IPD studies**

## All-cause mortality outcome

**Table 1. Two-stage IPD meta-analysis for mortality from any cause**

| Outcome | Number of studies | Testosterone treatment | Placebo |
|---|---|---|---|
| Mortality from any cause[1] | 21 | 11/2367 (0·5) | 18/2091 (0·9) |
| Details | | N=11 | N=18 |
| Myocardial Infarction | 4 | 2 (18·2) | 3 (16·7) |
| Cancer | 1 | 0 (0) | 3 (16·7) |
| Ruptured Aortic Aneurysm | 1 | 0 (0) | 1 (5·5) |
| Constrictive Pericarditis | 1 | 1 (16·7) | 0 (0) |
| Coronary Heart Disease | 1 | 1 (9·1) | 0 (0) |
| Multiple Organ Failure | 1 | 1 (9·1) | 0 (0) |
| Arrhythmia | 1 | 1 (9·1) | 0 (0) |
| Post-operative septicaemia | 1 | 0 (0) | 1 (5·5) |
| Venous thromboembolism | 1 | 0 (0) | 1 (5·5) |
| Unknown | 3 | 5 (45·5) | 9 (50·0) |

Values are numbers (percent) or numbers; OR Odds Ratio; CI Confidence Interval; [1]Of the 21 studies, 10 reported no deaths (Amory2004, Brock2016, Emmelot-Vonk2008, Giantti2014a, Groti2018, Hildreth2013, Kaufman2011a, Magnussen2016, Merza2006, Paduch2015a and Srinivas-Shankar2010).

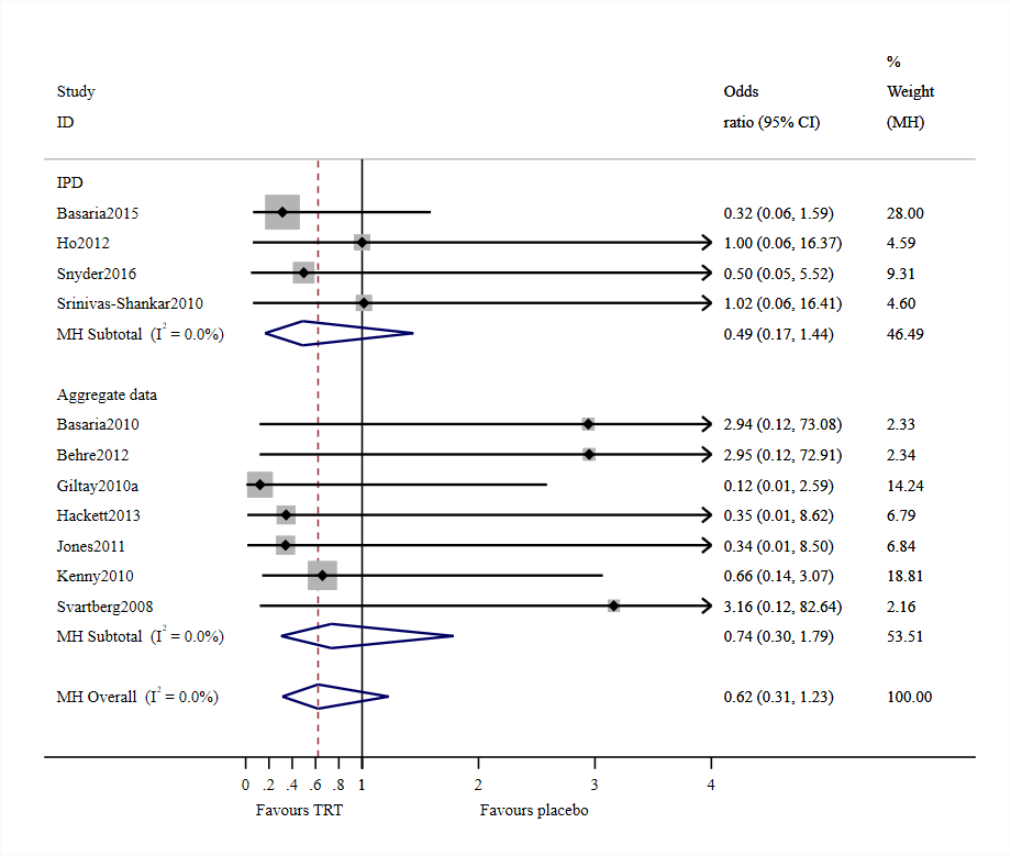



**Figure 1. IPD meta-analysis for mortality from any cause Mantel-Haenszel**

REML Restricted Maximum Likelihood; MH Mantel-Haenszel; TRT Testosterone Replacement Therapy; CI Confidence Interval.

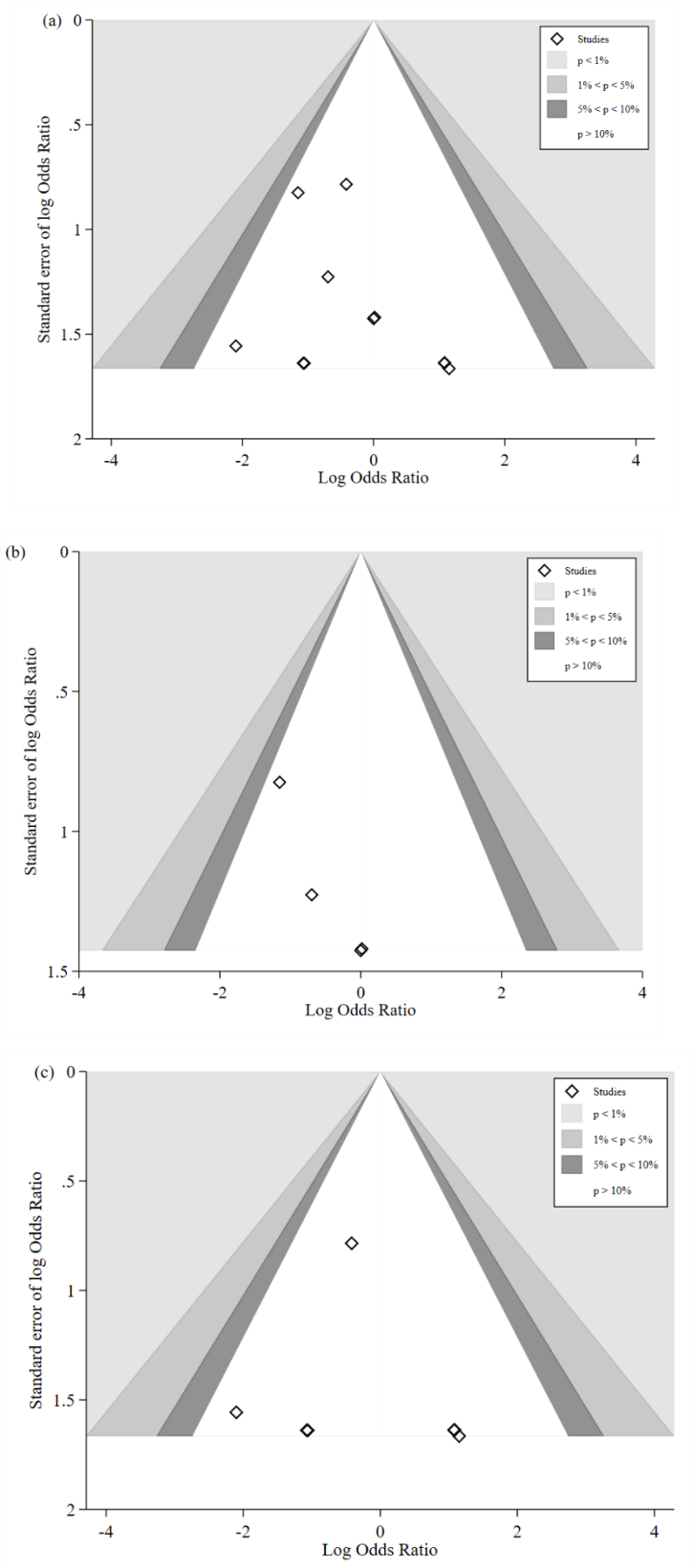



**Figure 2. Contour-enhanced funnel plot for mortality from any cause. (a) IPD and aggregate data; (b) IPD only; and (c) aggregate data only.**

## Cardiovascular and/or cerebrovascular primary outcome

**Table 1. Two-stage IPD meta-analysis for cardiovascular and/or cerebrovascular events**

| Outcome | Number of studies | Testosterone treatment | Placebo |
|---|---|---|---|
| Cardiovascular and/or cerebrovascular events[1] | 22 | 123/2496 (4·9) | 116/2073 (5·6) |
| Number of participants with a cardiovascular event | 20 | 110/123 (89·4) | 111/116 (95·7) |
| Total number of cardiovascular events[2] | 20 | 169 | 182 |
| Details | | | |
| Arrhythmia | 7 | 53 (31·4) | 47 (25·8) |
| Coronary Heart Disease | 7 | 34 (20·1) | 33 (18·1) |
| Heart Failure | 7 | 23 (13·6) | 28 (15·4) |
| Myocardial Infarction | 10 | 10 (5·9) | 19 (10·4) |
| Valvular Heart Disease | 2 | 18 (10·7) | 12 (6·6) |
| Peripheral Vascular Disease | 4 | 8 (4·7) | 14 (7·7) |
| Stable Angina | 5 | 7 (4·1) | 7 (3·8) |
| Aortic Aneurysm | 6 | 6 (3·6) | 8 (4·4) |
| New Angina | 3 | 5 (3·0) | 5 (2·7) |
| Unstable Angina | 3 | 2 (1·2) | 4 (2·2) |
| Aortic Dissection | 1 | 2 (1·2) | 0 (0) |
| Atherosclerosis | 1 | 1 (0·6) | 1 (0·5) |
| Cardiac Arrest | 2 | 0 (0) | 2 (1·1) |
| Angina | 1 | 0 (0) | 1 (0·5) |
| Open heart surgery | 1 | 0 (0) | 1 (0·5) |
| Number of participants with a cerebrovascular event | 11 | 15/120 (12·5) | 7/110 (6·4) |
| Total number of cerebrovascular events[2] | 11 | 16 | 7 |

Values are numbers (percent) or numbers. TRT Testosterone Replacement Therapy; OR Odds Ratio; CI Confidence Interval; [1]Of the 22 studies, five (Groti2018, Kaufman2011a, Magnussen2016, Paduch2015a and Steidle2003) reported no cardiovascular and/or cerebrovascular events. [2]Some participants had more than one event.

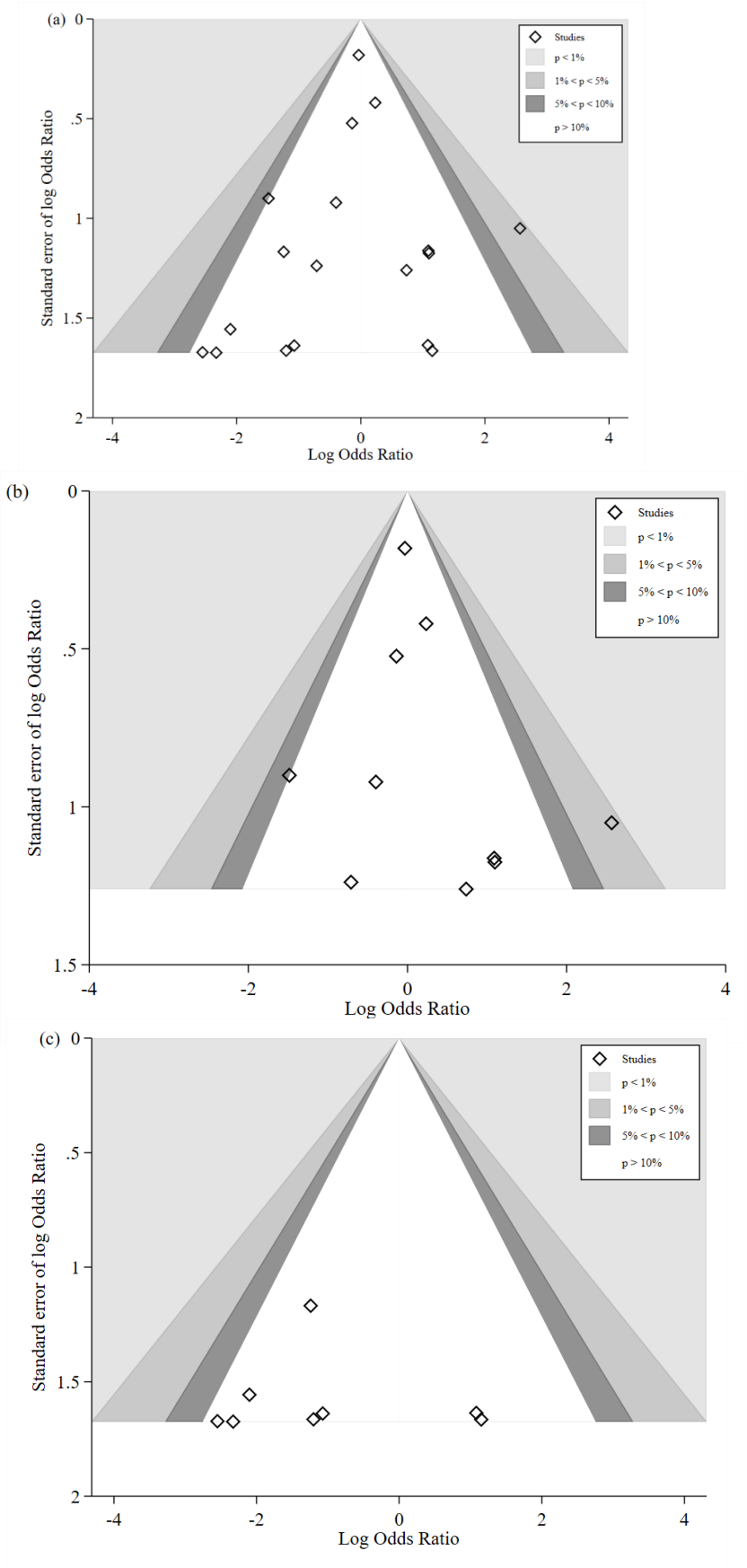



**Figure 1. Contour-enhanced funnel plot for Cardiovascular and/or cerebrovascular events. (a) IPD and aggregate data; (b) IPD only; and (c) aggregate data only.**

## Subgroup analyses

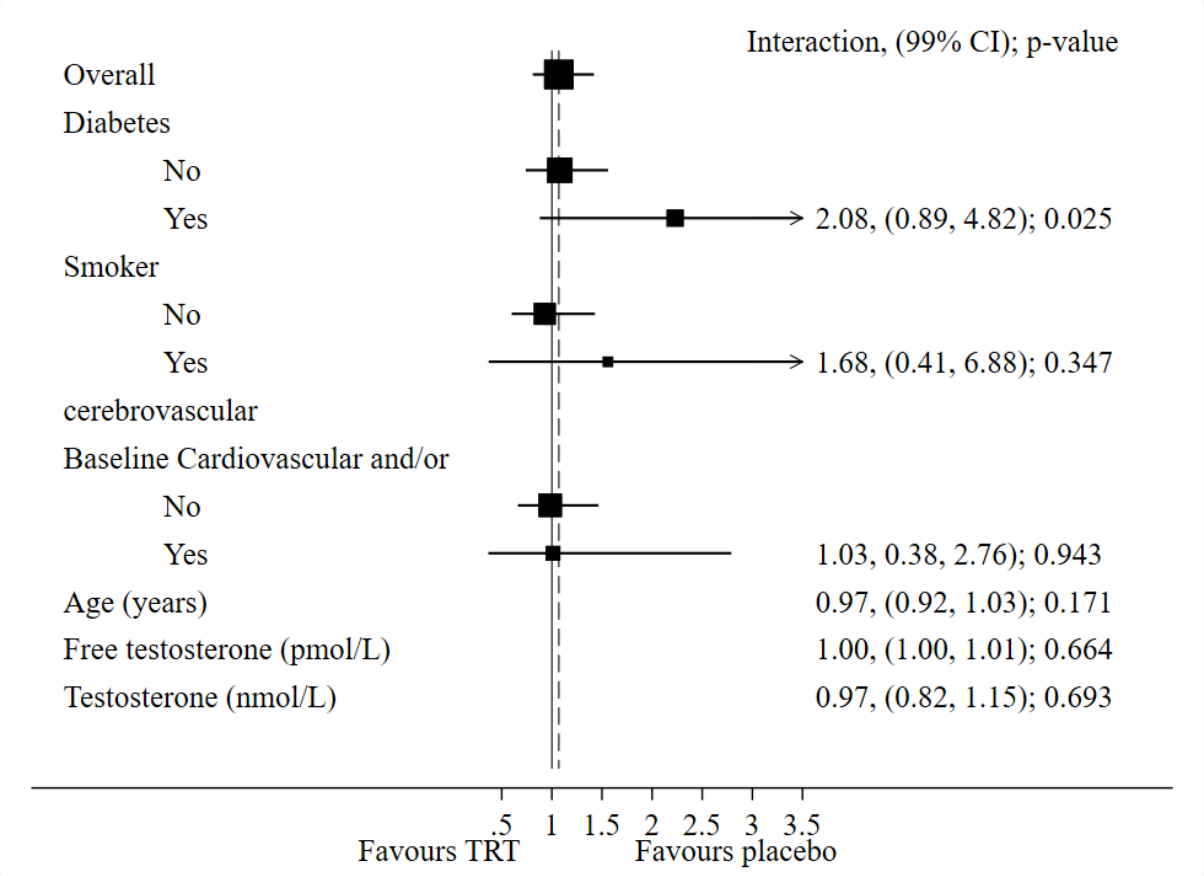



**Figure 1. Cardiovascular and/or cerebrovascular subgroups analysis for TRT versus placebo.**

TRT Testosterone Replacement Therapy; CI Confidence Interval.

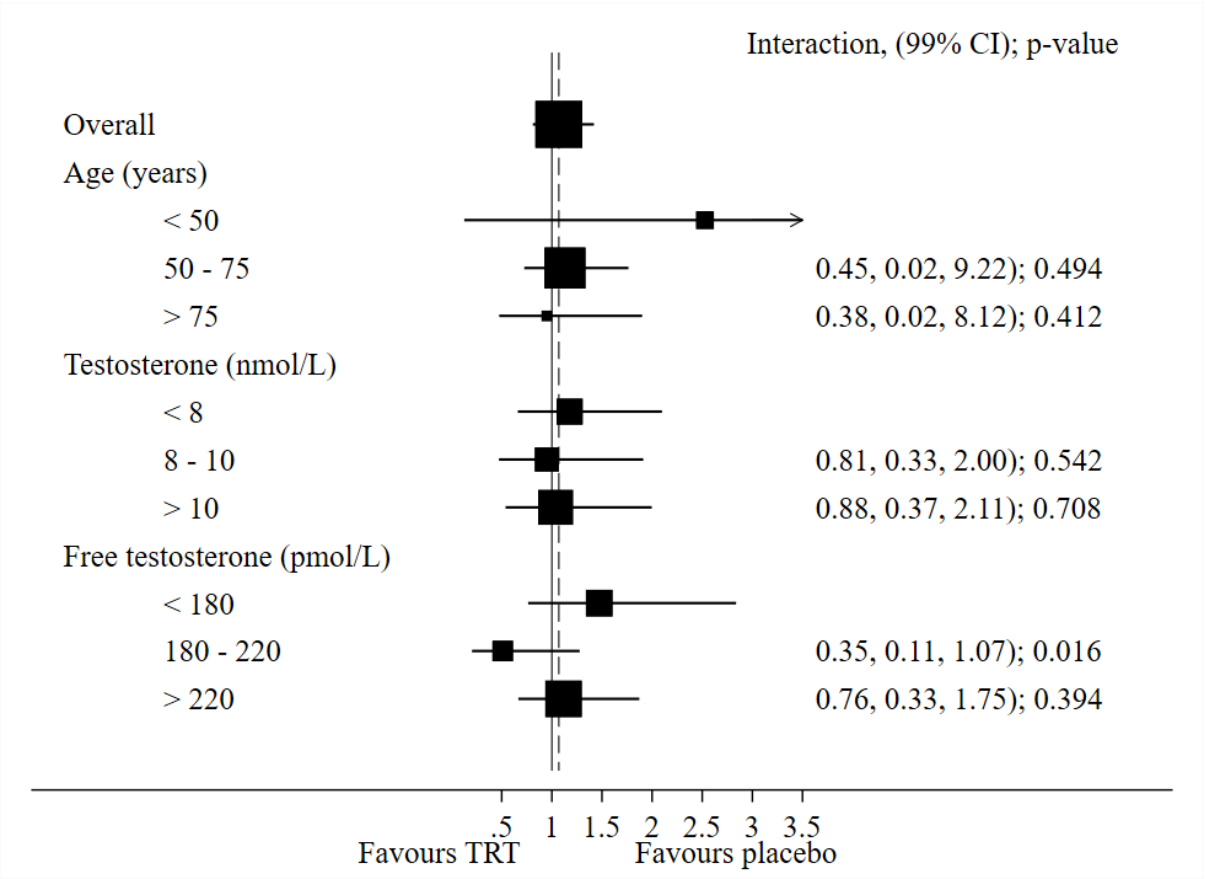



**Figure 2. Cardiovascular and/or cerebrovascular subgroups analysis for testosterone treatment versus placebo, according to age, testosterone level and free testosterone level.**

TRT Testosterone Replacement Therapy; CI Confidence Interval.

## One-stage meta-analysis

### Table 1. One-stage analysis for Physiological Marker outcomes

| Outcome | Number of studies | Testosterone treatment | Placebo | MD | 95% CI | $\tau^2$ |
|---|---|---|---|---|---|---|
| Areal bone mineral density (g/cm2) | | | | | | |
| Total | 4 | 1·21 (0·12); 352 | 1·20 (0·12); 312 | 0·00 | (-0·00, 0·01) | 0·00 |
| Sub-total | 2 | 1·03 (0·10); 108 | 1·02 (0·09); 103 | 0·00 | (-0·00, 0·01) | 0·00 |
| Femoral neck | 6 | 0·84 (0·14); 247 | 0·86 (0·16); 202 | -0·00 | (-0·01, 0·01) | 0·00 |
| Lumbar spine | 9 | 1·19 (0·21); 484 | 1·18 (0·21); 436 | 0·01 | (0·00, 0·02) | 0·00 |
| Thoracic spine | 2 | 0·96 (0·17); 154 | 0·92 (0·13); 132 | 0·01 | (-0·01, 0·03) | 0·00 |
| Total hip | 8 | 1·03 (0·15); 372 | 1·04 (0·15); 322 | 0·00 | (-0·00, 0·01) | 0·00 |
| Trochanter | 3 | 0·79 (0·13); 86 | 0·76 (0·11); 62 | 0·00 | (-0·01, 0·01) | 0·00 |
| Intertrochanter | 2 | 2·06 (5·55); 37 | 1·16 (0·16); 37 | 0·01 | (-0·00, 0·03) | 0·00 |
| Pelvis | 2 | 1·23 (0·19); 148 | 1·19 (0·18); 116 | 0·01 | (-0·00, 0·02) | 0·00 |
| Left arm | 3 | 0·85 (0·12); 175 | 0·83 (0·07); 151 | -0·00 | (-0·02, 0·01) | 0·00 |
| Right arm | 3 | 0·86 (0·13); 175 | 0·83 (0·08); 152 | 0·00 | (-0·00, 0·01) | 0·00 |
| Left plus right arm | 1 | 1·64 (0·13); 20 | 1·58 (0·40); 19 | -0·00 | (-0·02, 0·01) | |
| Left leg | 3 | 1·26 (0·18); 166 | 1·23 (0·11); 135 | 0·00 | (-0·01, 0·01) | 0·00 |
| Right leg | 3 | 1·26 (0·14); 162 | 1·25 (0·15); 132 | 0·01 | (0·00, 0·02) | 0·00 |
| Left plus right leg | 1 | 2·45 (0·29); 20 | 2·31 (0·63); 18 | 0·02 | (-0·03, 0·07) | |
| Left rib | 2 | 0·71 (0·09); 153 | 0·68 (0·08); 130 | 0·01 | (-0·00, 0·02) | 0·00 |
| Right rib | 2 | 0·72 (0·09); 155 | 0·69 (0·07); 134 | -0·00 | (-0·01, 0·01) | 0·00 |
| Head | 2 | 2·13 (0·32); 156 | 2·05 (0·33); 134 | 0·00 | (-0·02, 0·02) | 0·00 |
| Shaft | 1 | 1·21 (0·18); 47 | 1·15 (0·14); 23 | 0·00 | (-0·01, 0·02) | |
| Wards | 1 | 0·61 (0·17); 47 | 0·56 (0·12); 23 | -0·01 | (-0·03, 0·01) | |
| Volumetric bone mineral density (mg/cm3) | | | | | | |
| Spine trabecular | 1 | 106·78 (32·37); 104 | 99·61 (27·07); 85 | 6·32 | (4·54, 8·09) | |
| Spine cortical | 1 | 292·85 (43·05); 104 | 288·37 (43·83); 85 | 8·05 | (5·83, 10·28) | |
| Spine whole | 1 | 199·57 (37·21); 104 | 194·61 (34·75); 85 | 7·86 | (5·98, 9·74) | |
| Hips trabecular | 1 | 187·12 (35·03); 99 | 181·87 (32·92); 79 | 2·36 | (1·41, 3·31) | |
| Hips cortical | 1 | 402·83 (46·10); 99 | 395·65 (47·97); 79 | 3·52 | (1·52, 5·52) | |
| Hips whole | 1 | 251·22 (38·56); 09 | 245·19 (37·80); 79 | 2·84 | (1·71, 3·97) | |

Values are mean (Standard deviation); numbers. TRT Testosterone Replacement Therapy; CI Confidence Interval; MD Mean Difference; A fixed effects analysis was used as only one study reported the outcome.

## Two-stage meta-analysis analysis

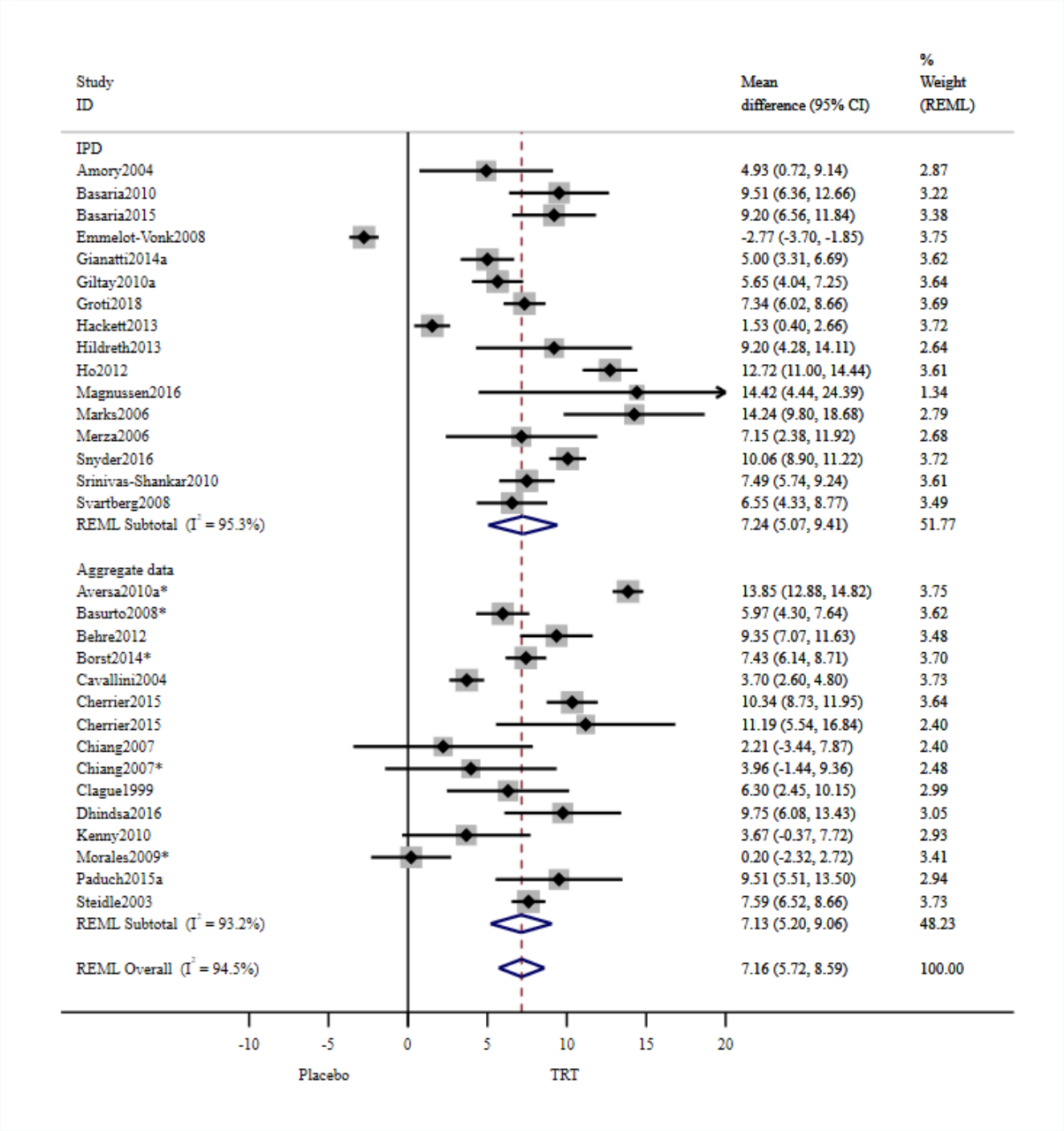



**Figure 1. Two-stage meta-analysis for increase in testosterone (nmol/L).**
CI Confidence Interval; TRT Testosterone Replacement Therapy; REML Restricted Maximum Likelihood.
*Data presented as change from baseline

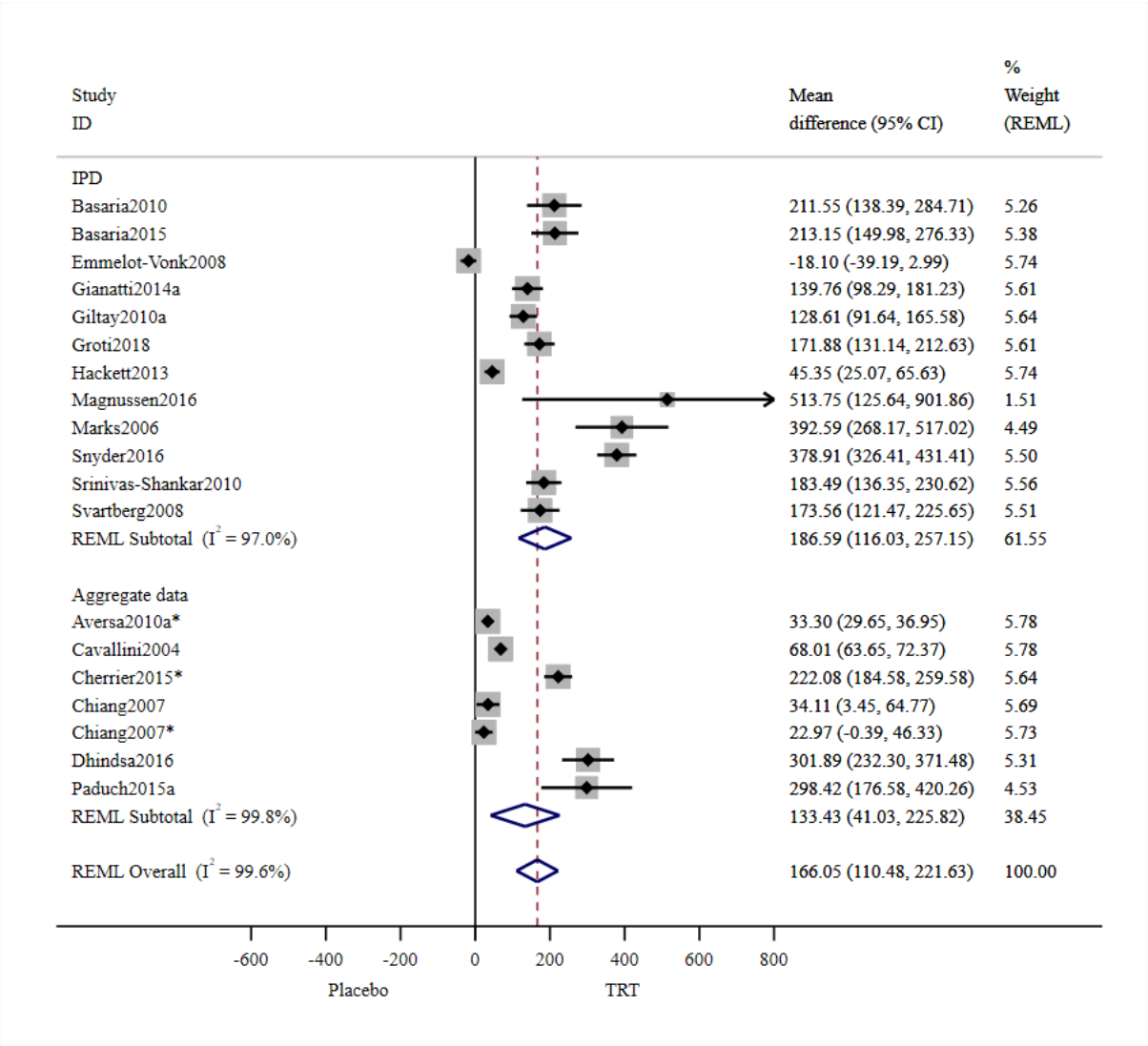



**Figure 2. Two-stage meta-analysis for increase in free testosterone (pmol/L).**

CI Confidence Interval; TRT Testosterone Replacement Therapy; REML Restricted Maximum Likelihood.

*Data presented as change from baseline

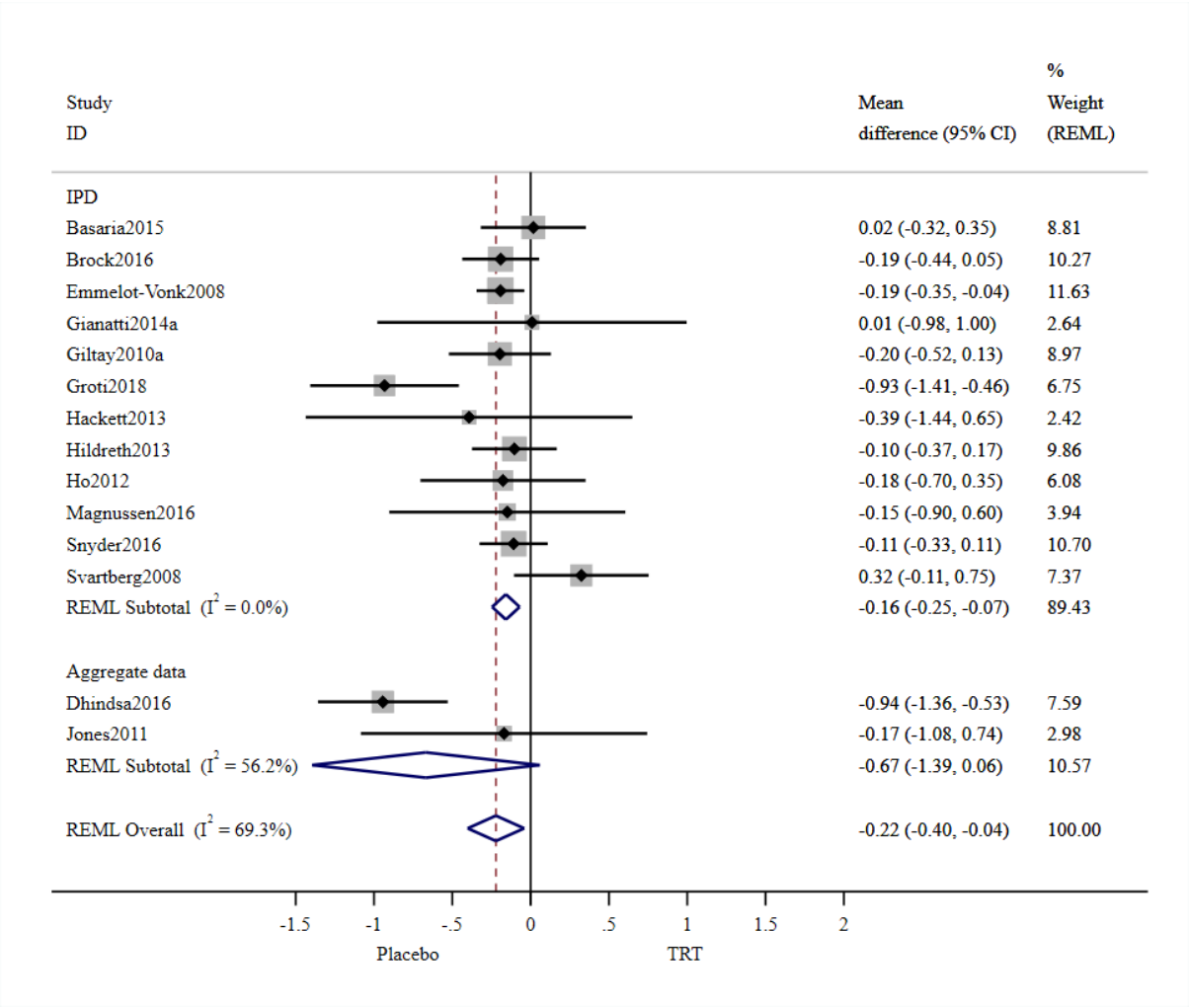



**Figure 3. Two-stage meta-analysis for increase in fasting glucose (mmol/L).**
CI Confidence Interval; TRT Testosterone Replacement Therapy; REML Restricted Maximum Likelihood.

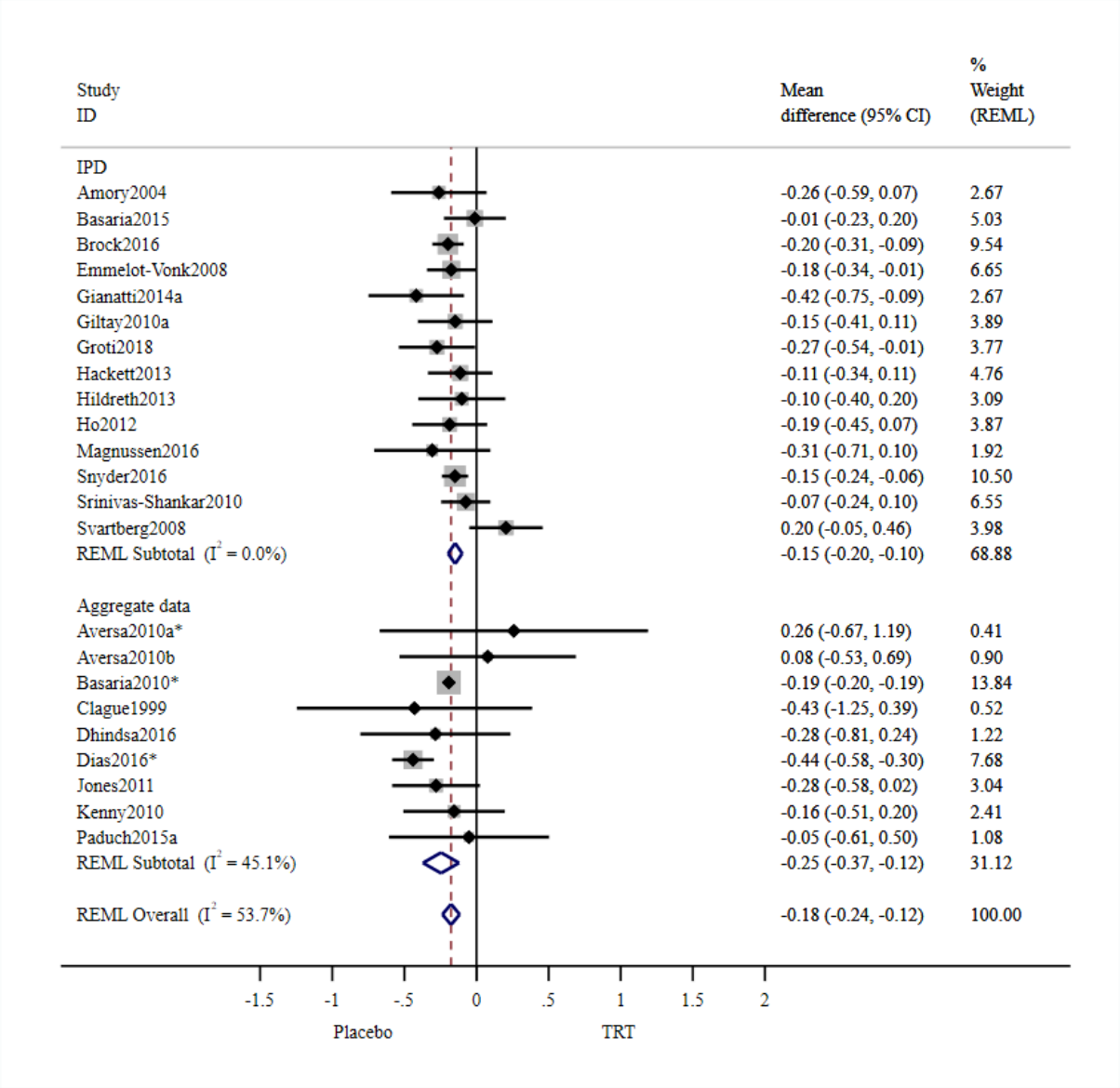



**Figure 4. Two-stage meta-analysis for increase in cholesterol (mmol/L).**

CI Confidence Interval; TRT Testosterone Replacement Therapy; REML Restricted Maximum Likelihood.
*Data presented as change from baseline

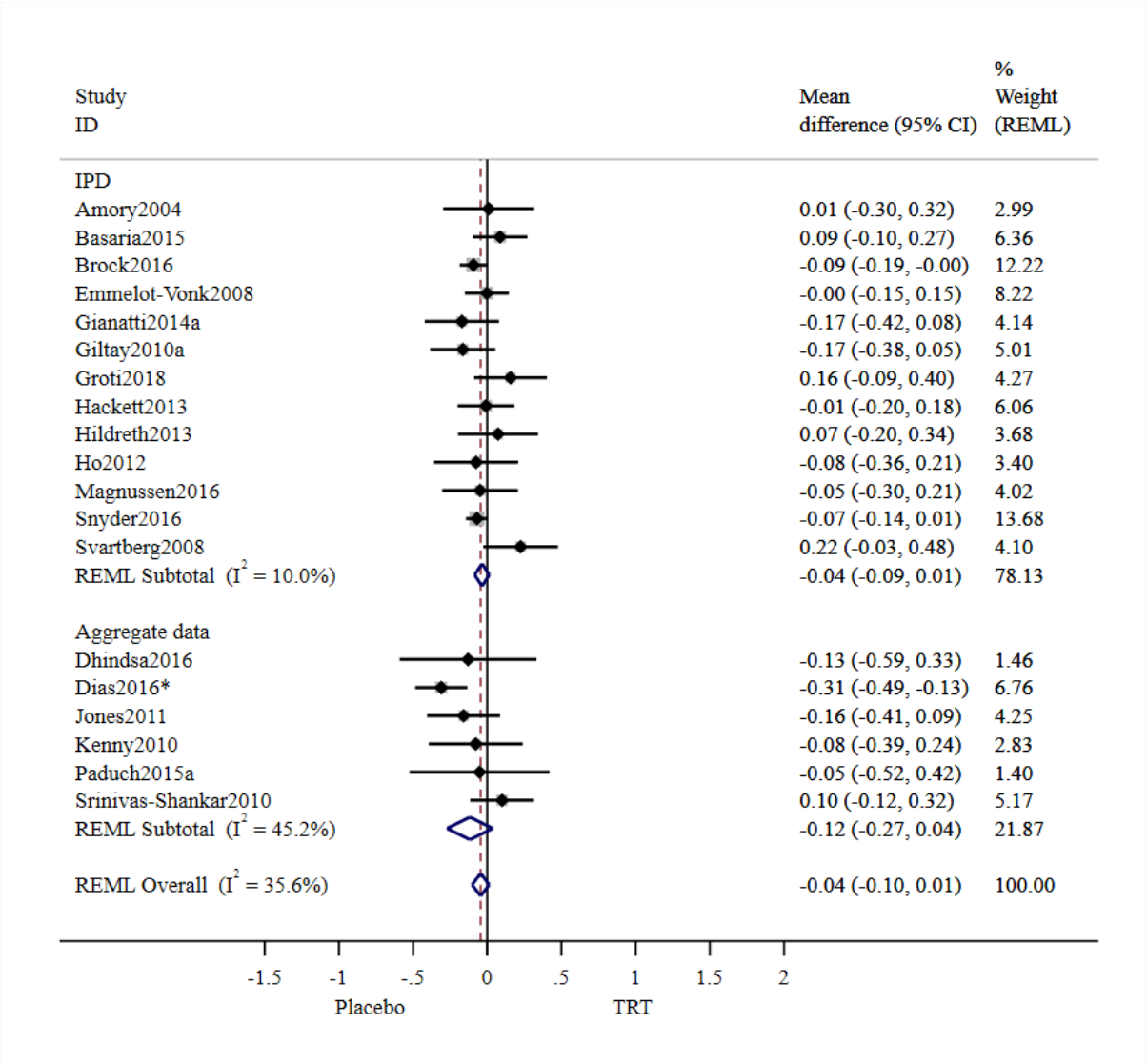



**Figure 5. Two-stage meta-analysis for increase in low-Density Lipoproteins cholesterol (mmol/L)**

CI Confidence Interval; TRT Testosterone Replacement Therapy; REML Restricted Maximum Likelihood.
*Data presented as change from baseline

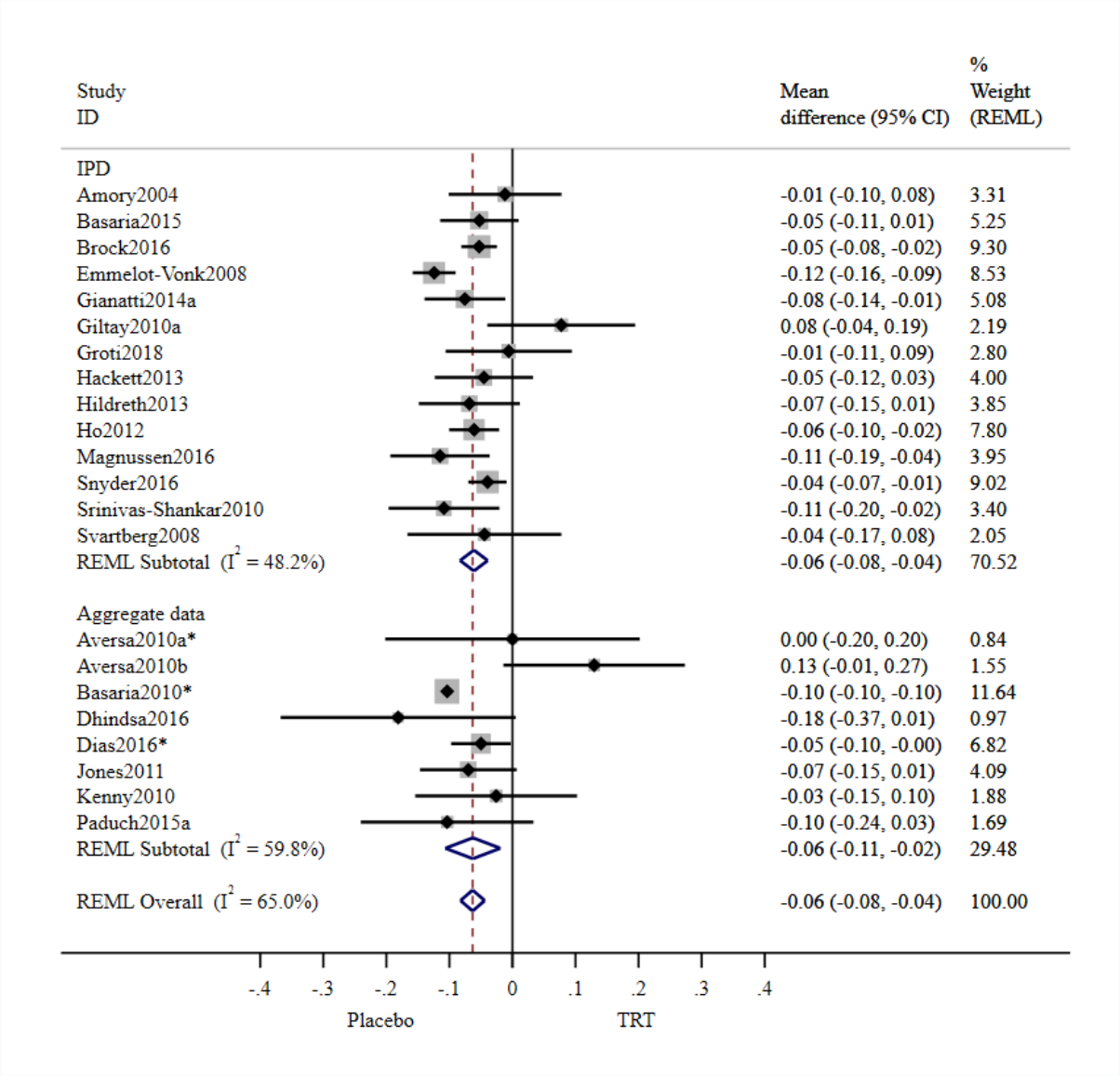



**Figure 6. Two-stage meta-analysis for increase in high-Density Lipoproteins cholesterol (mmol/L)**

CI Confidence Interval; TRT Testosterone Replacement Therapy; REML Restricted Maximum Likelihood.
*Data presented as change from baseline

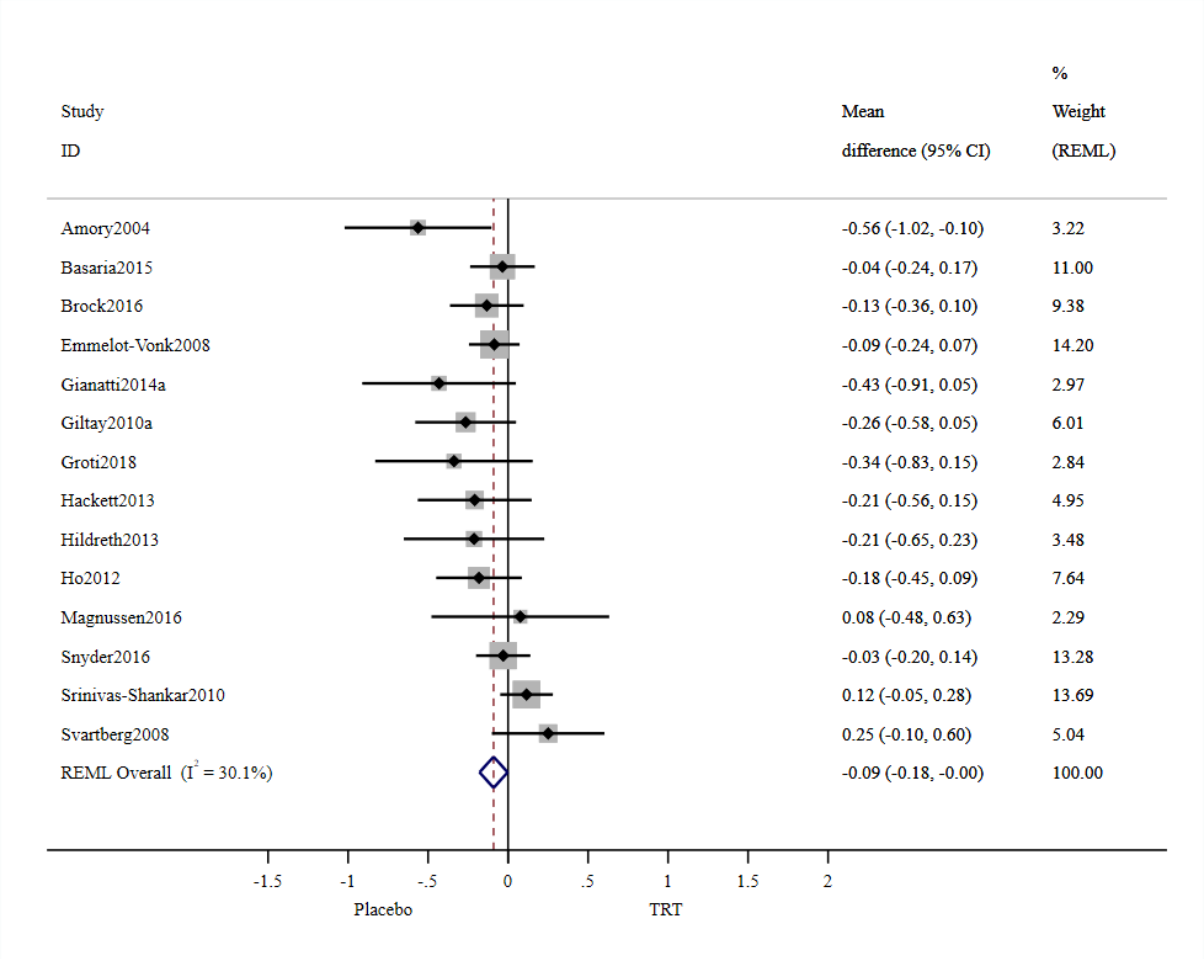



**Figure 7. Two-stage meta-analysis for increase in triglycerides (mmol/L)**

CI Confidence Interval; TRT Testosterone Replacement Therapy; REML Restricted Maximum Likelihood.

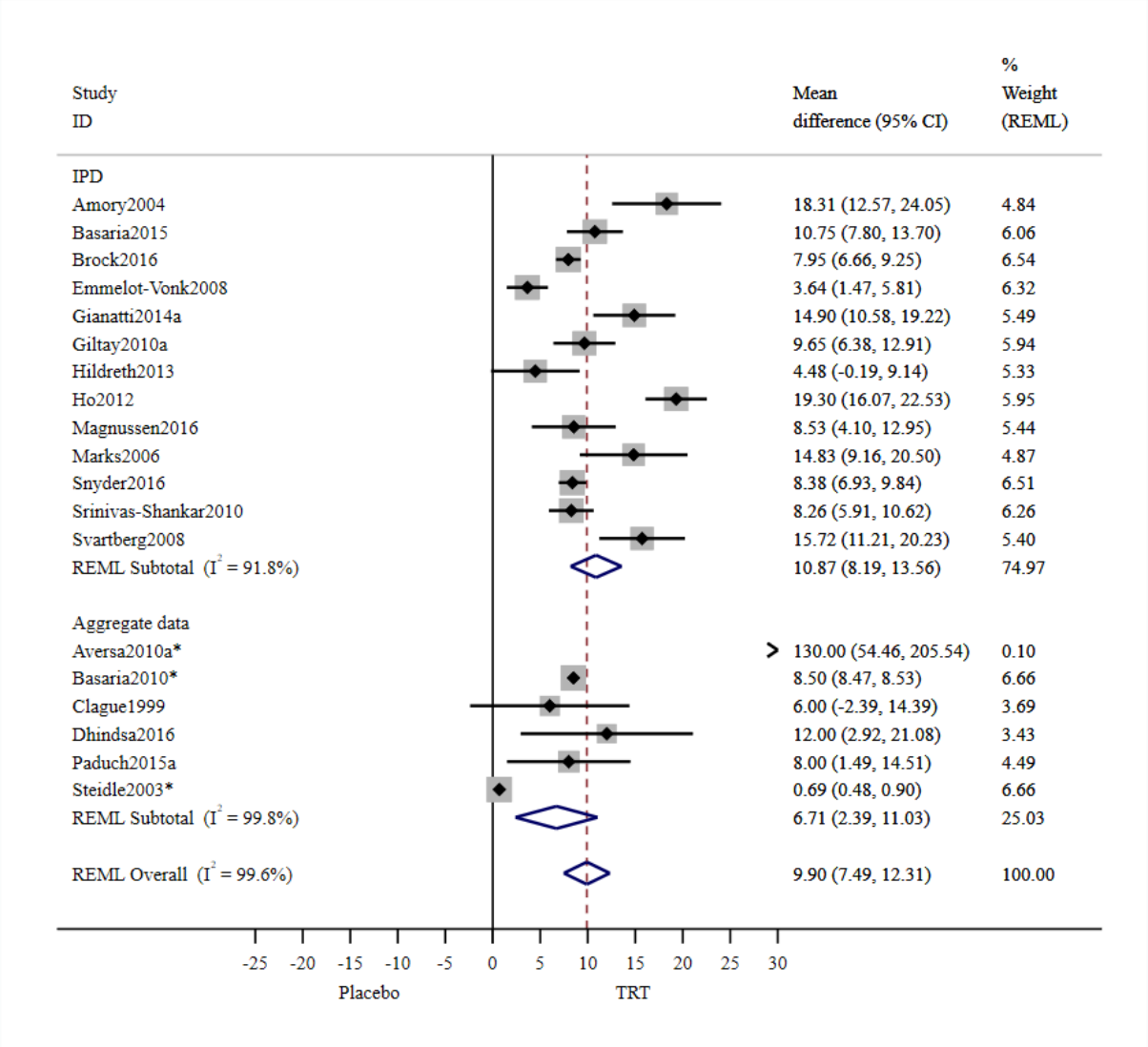



**Figure 8. Two-stage meta-analysis for increase in haemoglobin (g/L)**

CI Confidence Interval; TRT Testosterone Replacement Therapy; REML Restricted Maximum Likelihood.
*Data presented as change from baseline

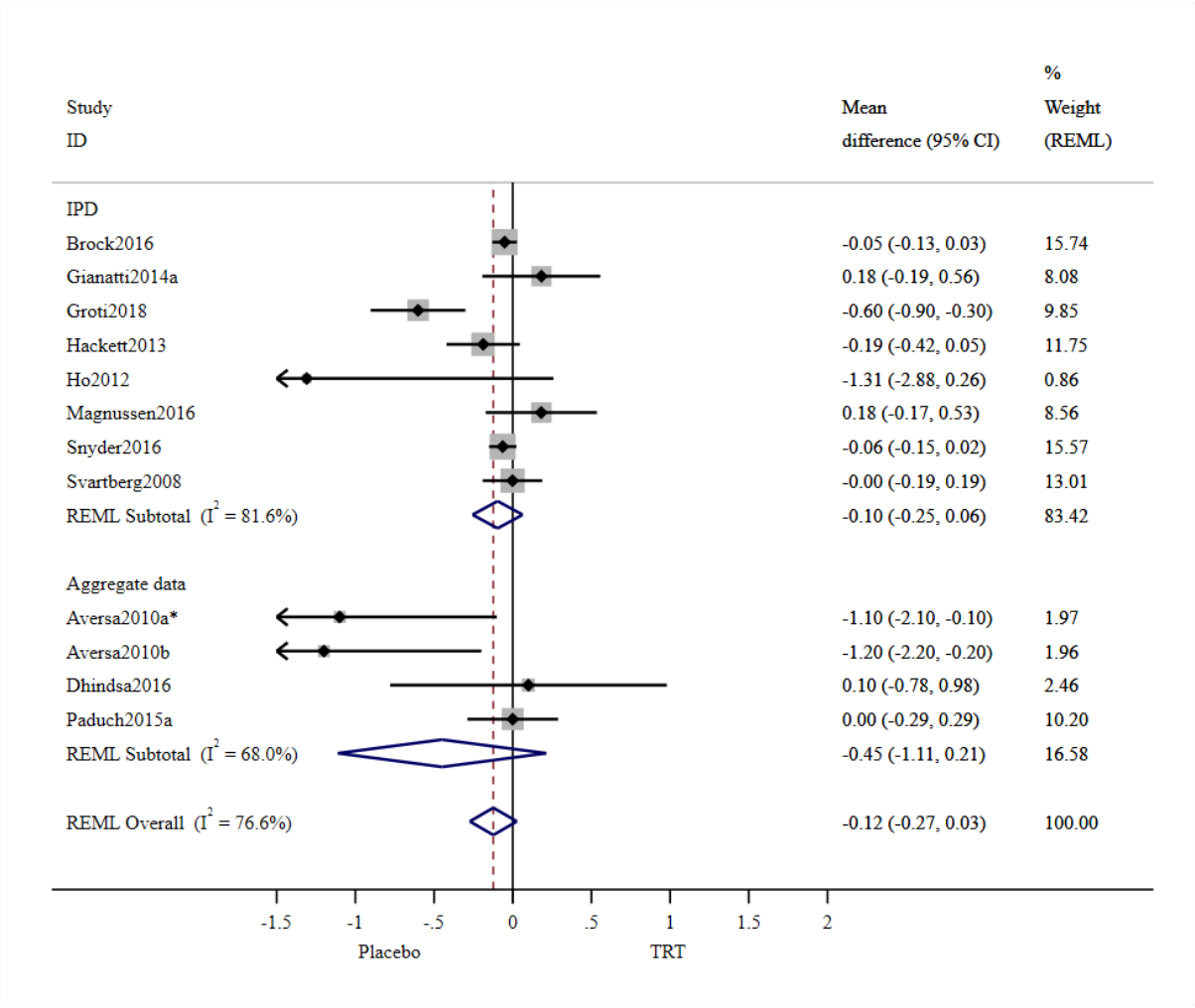



**Figure 9. Two-stage meta-analysis for increase in HbA1c (%)**

CI Confidence Interval; TRT Testosterone Replacement Therapy; REML Restricted Maximum Likelihood.
*Data presented as change from baseline

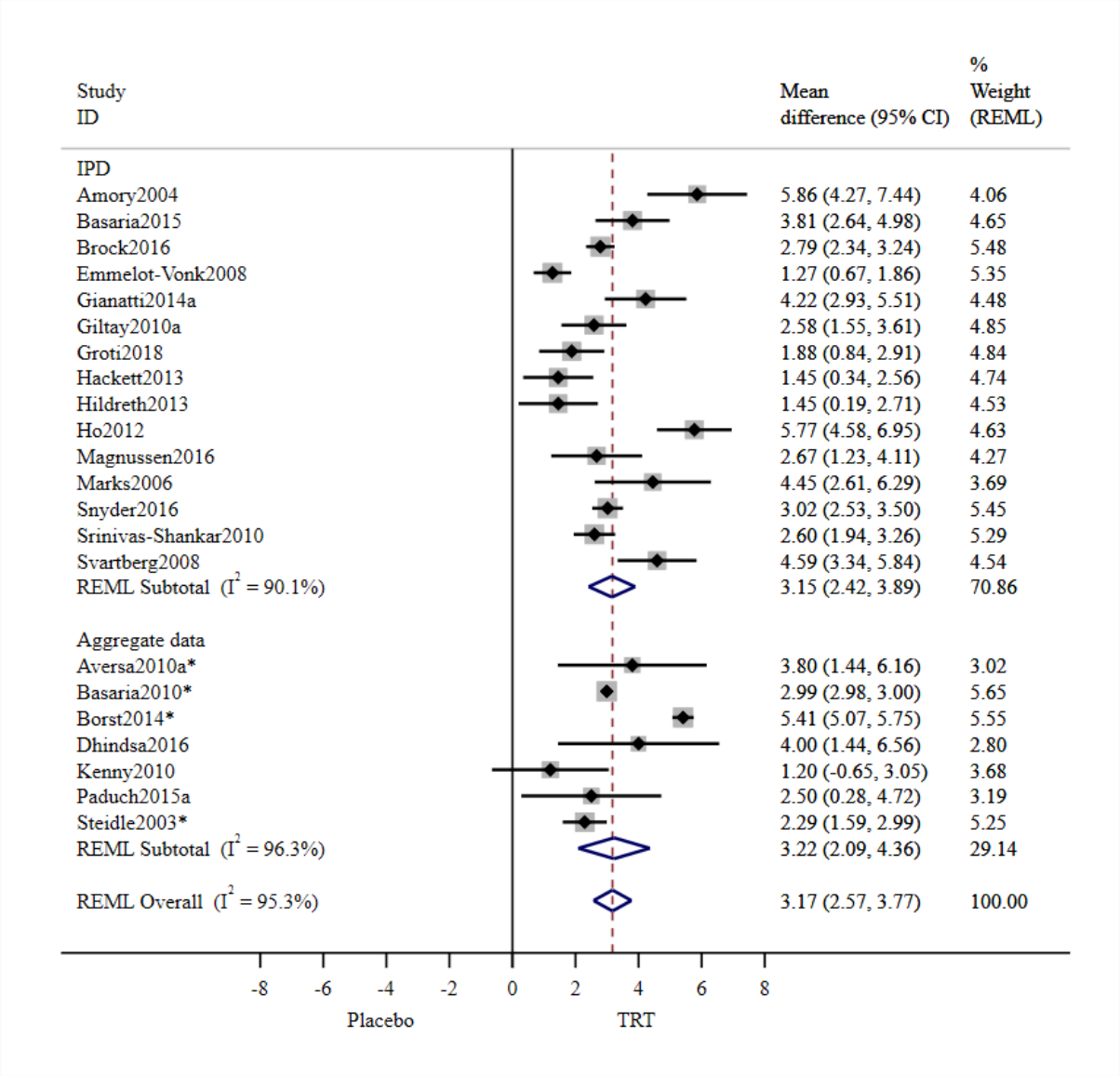



**Figure 10. Two-stage meta-analysis for increase in haematocrit (%)**

CI Confidence Interval; TRT Testosterone Replacement Therapy; REML Restricted Maximum Likelihood.
*Data presented as change from baseline

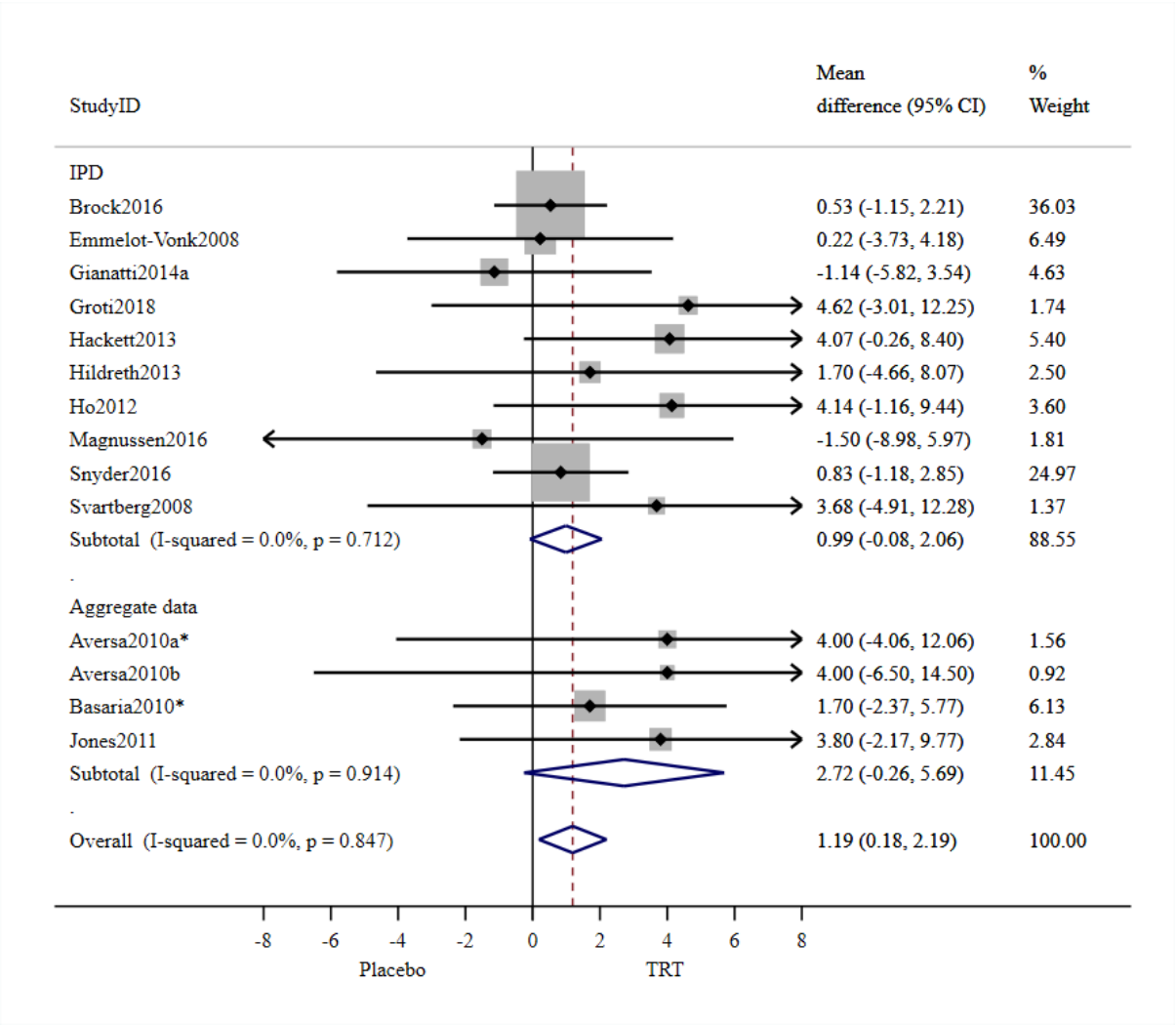



**Figure 11. Two-stage meta-analysis for increase in systolic blood pressure (mmHg)**

CI Confidence Interval; TRT Testosterone Replacement Therapy.

*Data presented as change from baseline

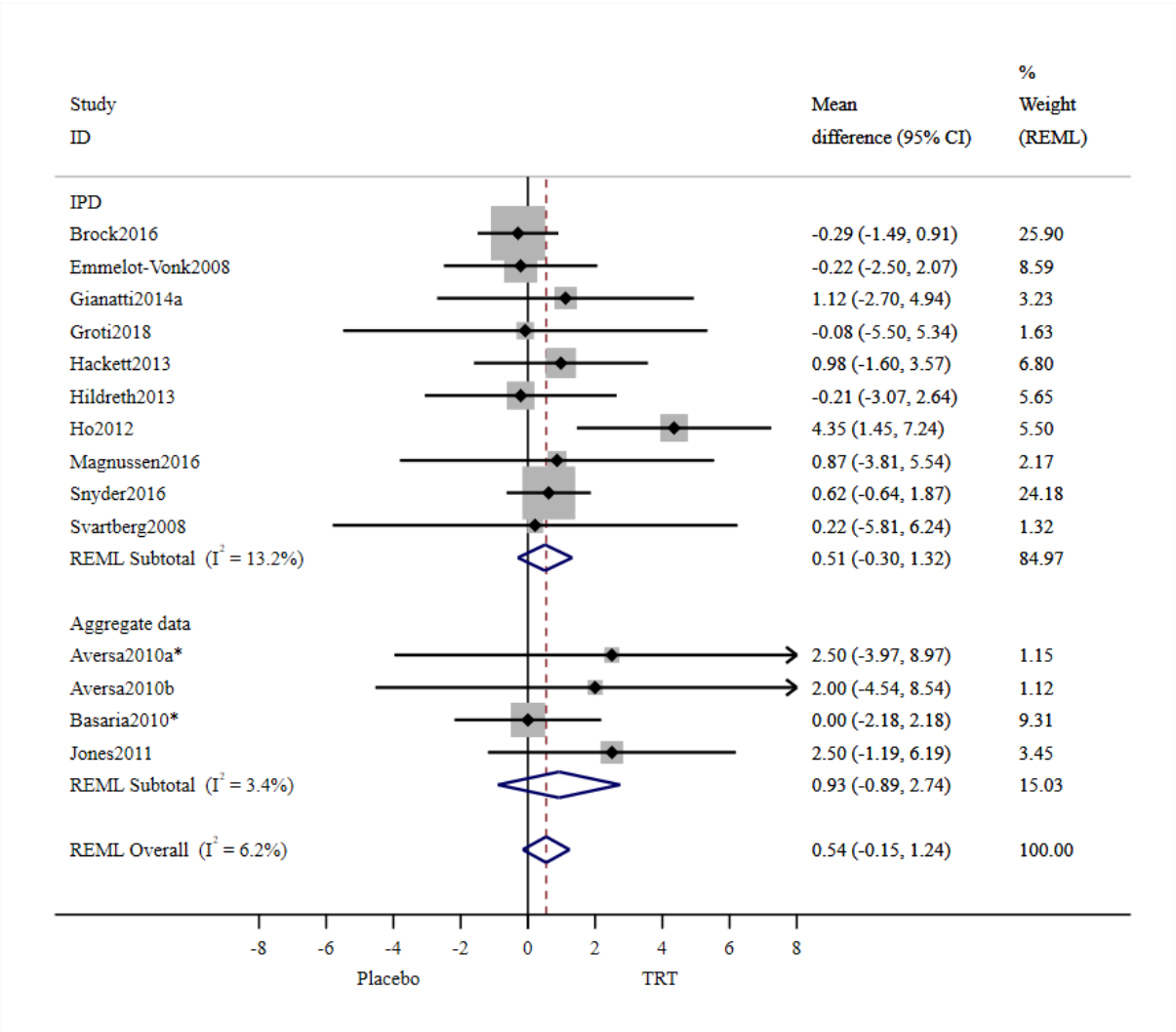
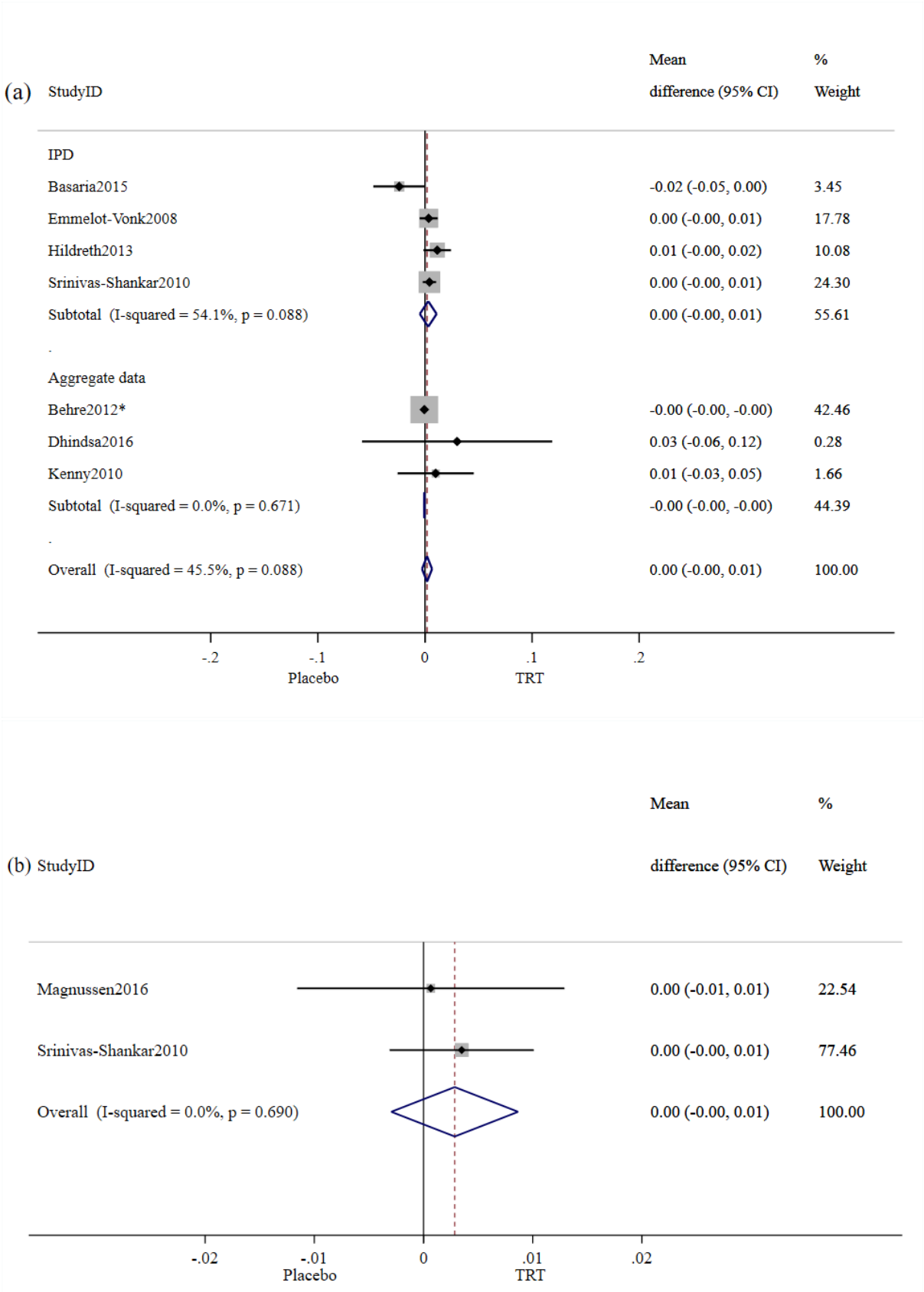
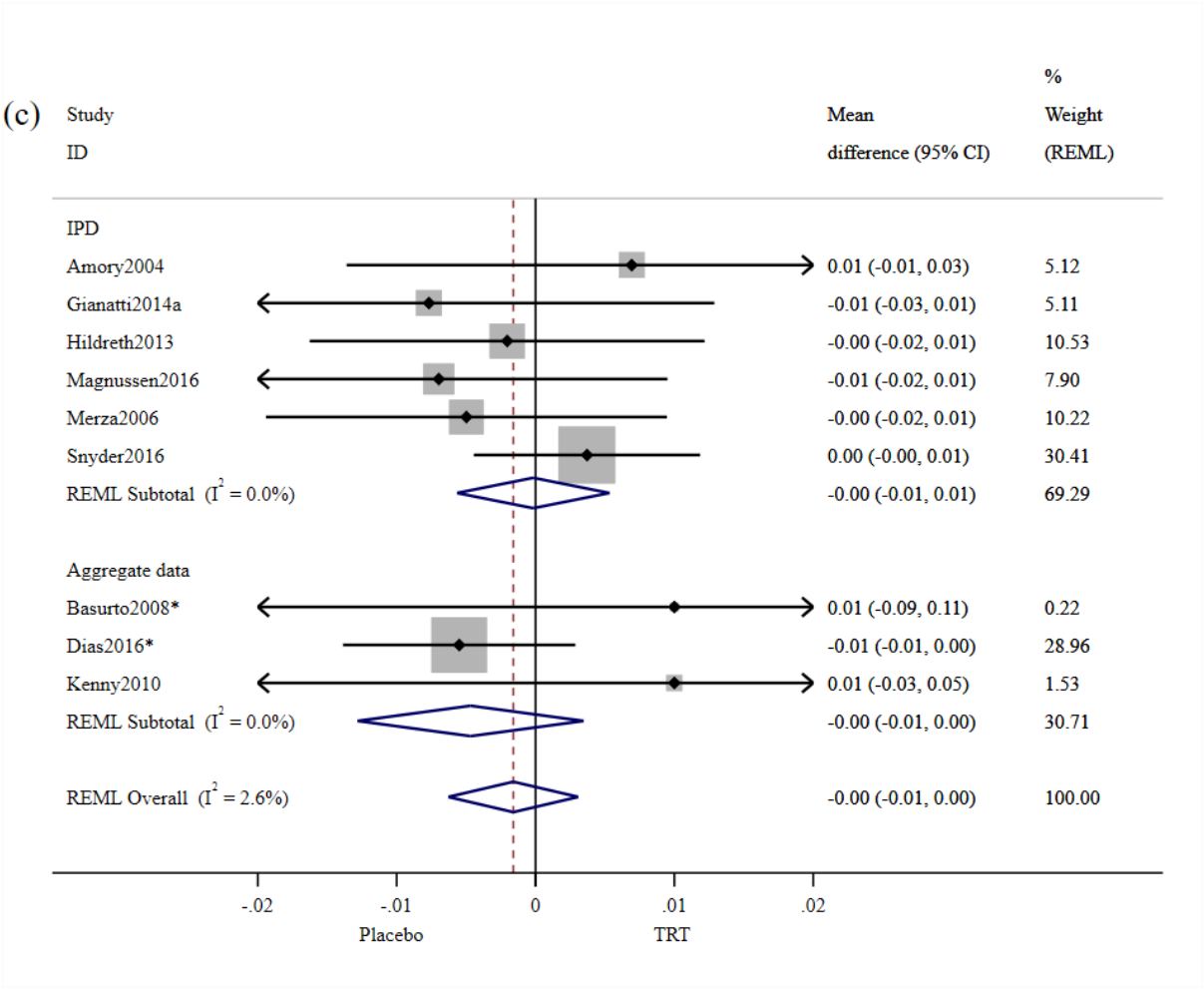
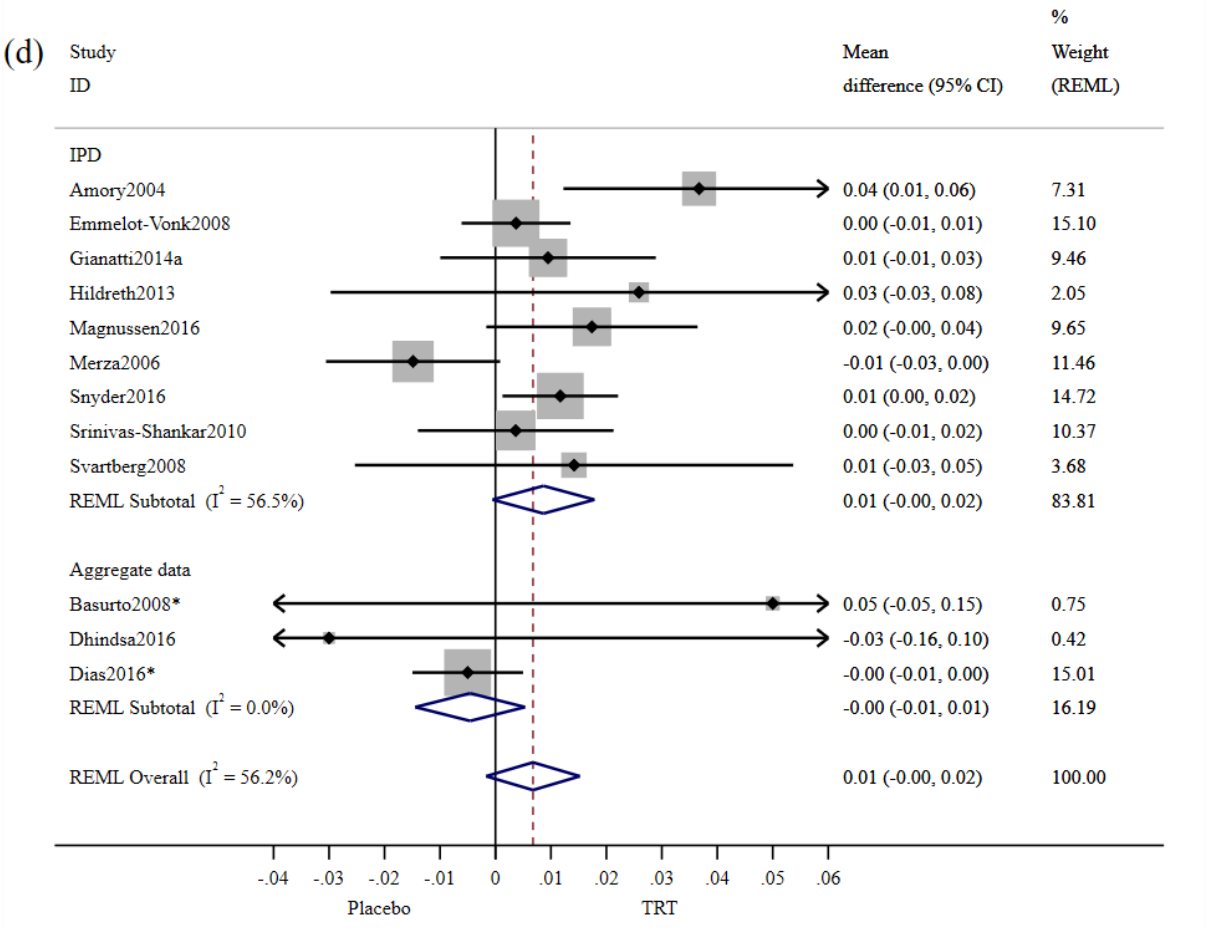


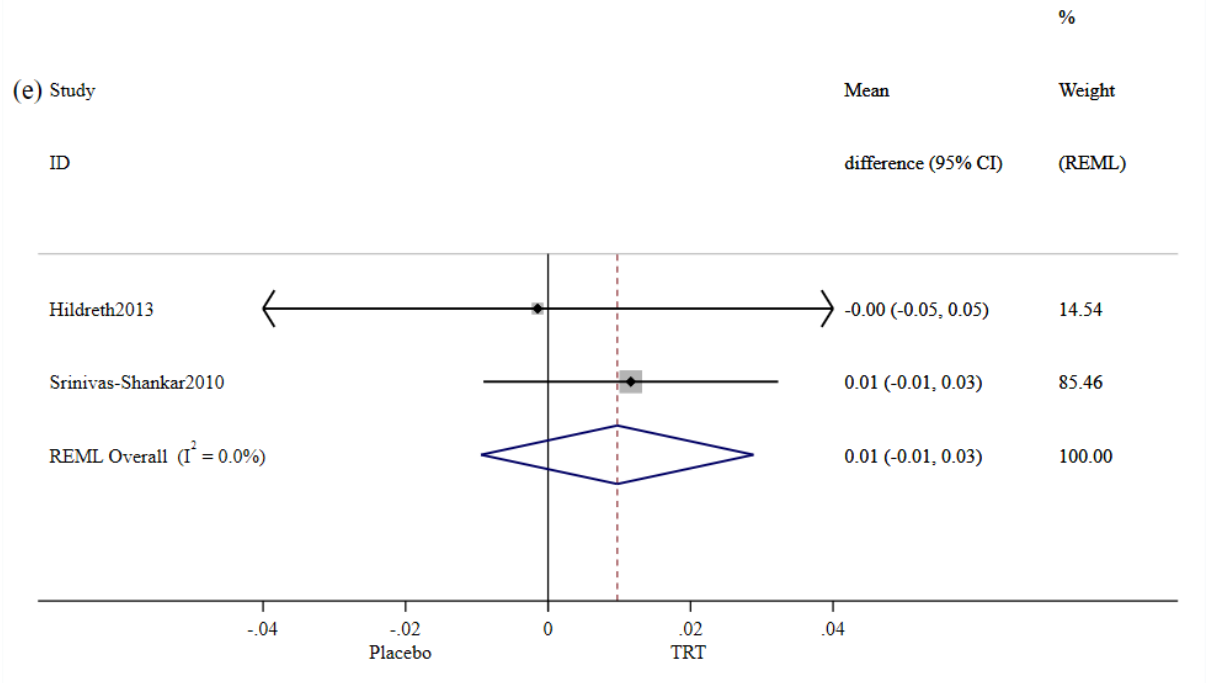

**Figure 12. Two-stage meta-analysis for increase in diastolic blood pressure (mmHg) (nmol/L)**

CI Confidence Interval; TRT Testosterone Replacement Therapy; REML Restricted Maximum Likelihood.
*Data presented as change from baseline

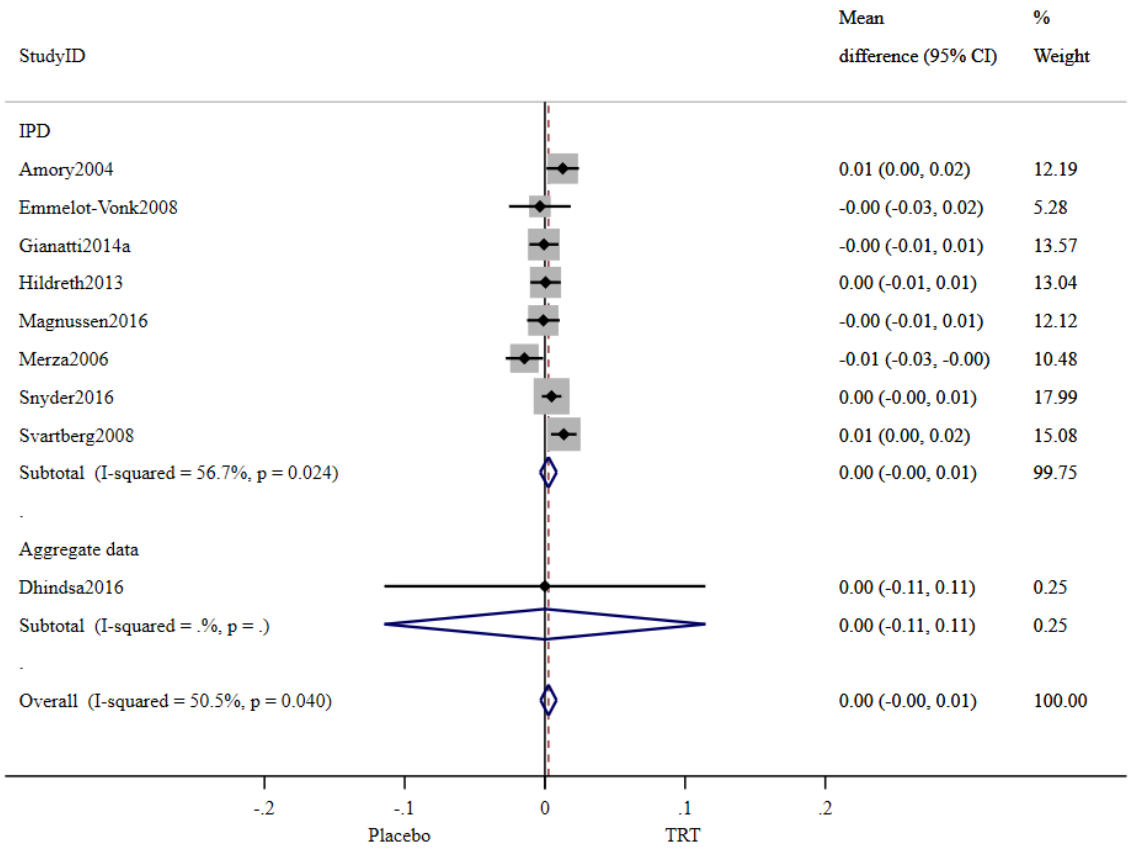

(a)
StudyID
Mean difference (95% CI)
%
Weight
IPD
Basaria2015
-0.02 (-0.05, 0.00)
3.45
Emmelot-Vonk2008
0.00 (-0.00, 0.01)
17.78
Hildreth2013
0.01 (-0.00, 0.02)
10.08
Srinivas-Shankar2010
0.00 (-0.00, 0.01)
24.30
Subtotal (I-squared = 54.1%, p = 0.088)
0.00 (-0.00, 0.01)
55.61
Aggregate data
Behre2012*
-0.00 (-0.00, -0.00)
42.46
Dhindsa2016
0.03 (-0.06, 0.12)
0.28
Kenny2010
0.01 (-0.03, 0.05)
1.66
Subtotal (I-squared = 0.0%, p = 0.671)
-0.00 (-0.00, -0.00)
44.39
Overall (I-squared = 45.5%, p = 0.088)
0.00 (-0.00, 0.01)
100.00
-.2
-.1
0
.1
.2
Placebo
TRT
(b)
StudyID
Mean difference (95% CI)
%
Weight
Magnussen2016
0.00 (-0.01, 0.01)
22.54
Srinivas-Shankar2010
0.00 (-0.00, 0.01)
77.46
Overall (I-squared = 0.0%, p = 0.690)
0.00 (-0.00, 0.01)
100.00
-.02
-.01
0
.01
.02
Placebo
TRT


(c)
Study ID
Mean difference (95% CI)
% Weight (REML)
IPD
Amory2004
0.01 (-0.01, 0.03)
5.12
Gianatti2014a
-0.01 (-0.03, 0.01)
5.11
Hildreth2013
-0.00 (-0.02, 0.01)
10.53
Magnussen2016
-0.01 (-0.02, 0.01)
7.90
Merza2006
-0.00 (-0.02, 0.01)
10.22
Snyder2016
0.00 (-0.00, 0.01)
30.41
REML Subtotal (I² = 0.0%)
-0.00 (-0.01, 0.01)
69.29
Aggregate data
Basurto2008*
0.01 (-0.09, 0.11)
0.22
Dias2016*
-0.01 (-0.01, 0.00)
28.96
Kenny2010
0.01 (-0.03, 0.05)
1.53
REML Subtotal (I² = 0.0%)
-0.00 (-0.01, 0.00)
30.71
REML Overall (I² = 2.6%)
-0.00 (-0.01, 0.00)
100.00
-.02
-.01
0
.01
.02
Placebo
TRT

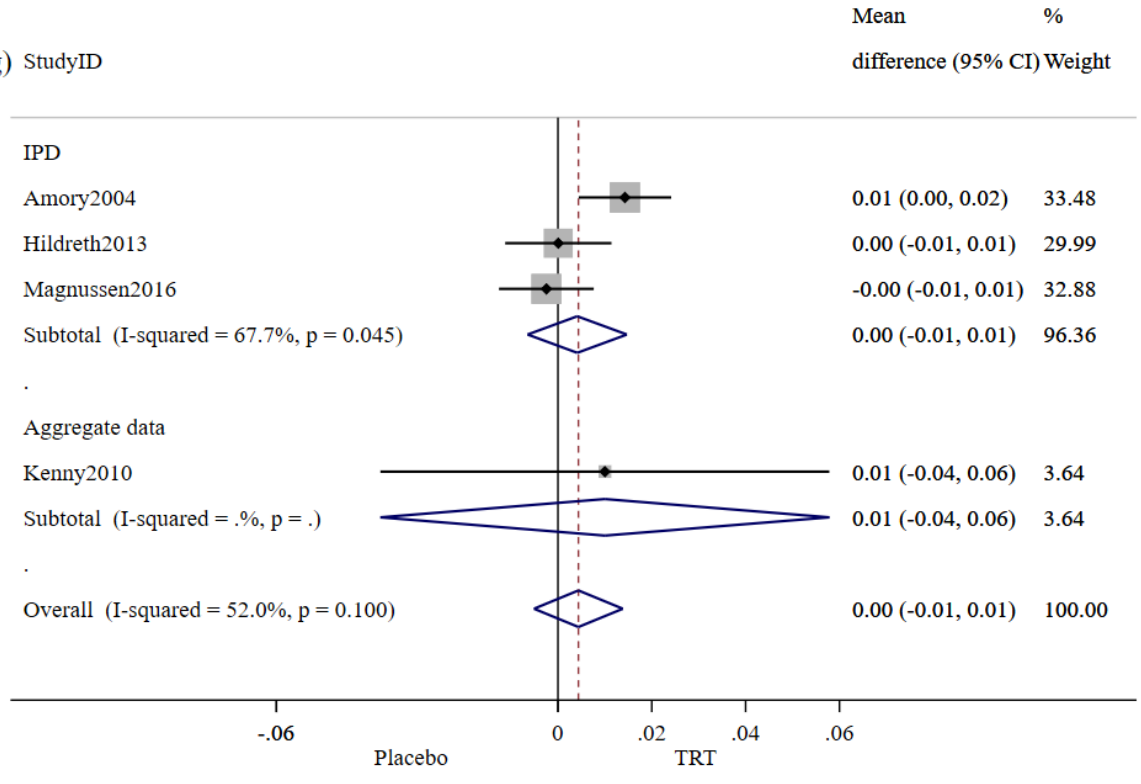

(d)
Study ID
Mean difference (95% CI)
% Weight (REML)
IPD
Amory2004 0.04 (0.01, 0.06) 7.31
Emmelot-Vonk2008 0.00 (-0.01, 0.01) 15.10
Gianatti2014a 0.01 (-0.01, 0.03) 9.46
Hildreth2013 0.03 (-0.03, 0.08) 2.05
Magnussen2016 0.02 (-0.00, 0.04) 9.65
Merza2006 -0.01 (-0.03, 0.00) 11.46
Snyder2016 0.01 (0.00, 0.02) 14.72
Srinivas-Shankar2010 0.00 (-0.01, 0.02) 10.37
Svartberg2008 0.01 (-0.03, 0.05) 3.68
REML Subtotal ($I^2$ = 56.5%) 0.01 (-0.00, 0.02) 83.81
Aggregate data
Basurto2008* 0.05 (-0.05, 0.15) 0.75
Dhindsa2016 -0.03 (-0.16, 0.10) 0.42
Dias2016* -0.00 (-0.01, 0.00) 15.01
REML Subtotal ($I^2$ = 0.0%) -0.00 (-0.01, 0.01) 16.19
REML Overall ($I^2$ = 56.2%) 0.01 (-0.00, 0.02) 100.00
-.04 -.03 -.02 -.01 0 .01 .02 .03 .04 .05 .06
Placebo
TRT

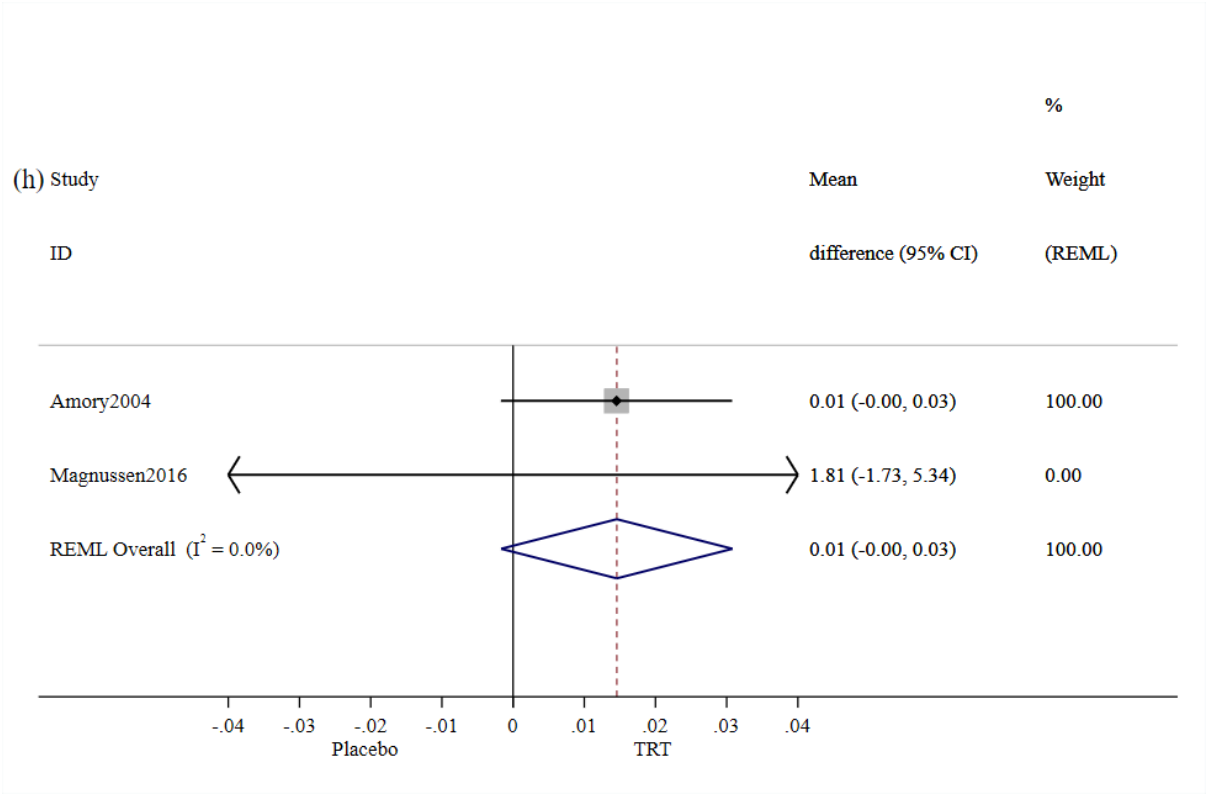

(e) Study ID
Mean difference (95% CI)
% Weight (REML)
Hildreth2013 -0.00 (-0.05, 0.05) 14.54
Srinivas-Shankar2010 0.01 (-0.01, 0.03) 85.46
REML Overall ($I^2$ = 0.0%) 0.01 (-0.01, 0.03) 100.00
-.04 -.02 0 .02 .04
Placebo
TRT

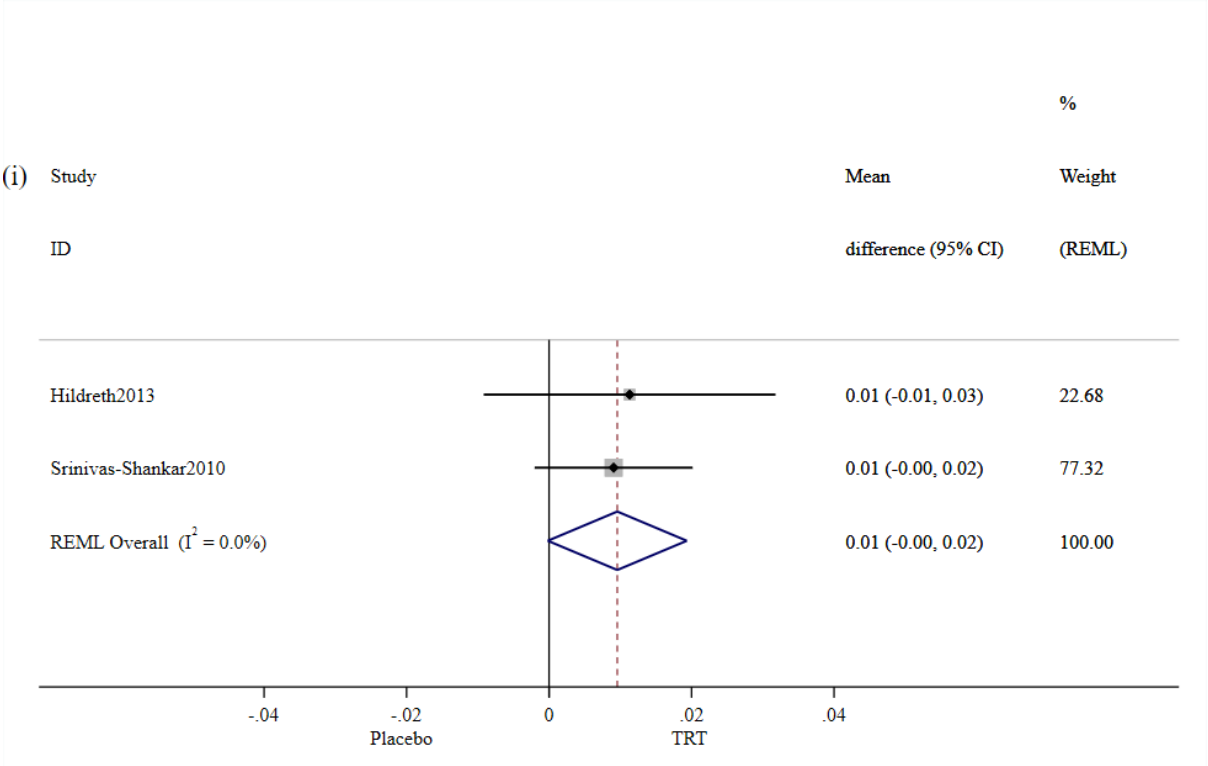
(f)


StudyID
Mean difference (95% CI)
% Weight
IPD
Amory2004 0.01 (0.00, 0.02) 12.19
Emmelot-Vonk2008 -0.00 (-0.03, 0.02) 5.28
Gianatti2014a -0.00 (-0.01, 0.01) 13.57
Hildreth2013 0.00 (-0.01, 0.01) 13.04
Magnussen2016 -0.00 (-0.01, 0.01) 12.12
Merza2006 -0.01 (-0.03, -0.00) 10.48
Snyder2016 0.00 (-0.00, 0.01) 17.99
Svartberg2008 0.01 (0.00, 0.02) 15.08
Subtotal (I-squared = 56.7%, p = 0.024) 0.00 (-0.00, 0.01) 99.75
Aggregate data
Dhindsa2016 0.00 (-0.11, 0.11) 0.25
Subtotal (I-squared = .%, p = .) 0.00 (-0.11, 0.11) 0.25
Overall (I-squared = 50.5%, p = 0.040) 0.00 (-0.00, 0.01) 100.00
-.2
-.1
0
.1
.2
Placebo
TRT

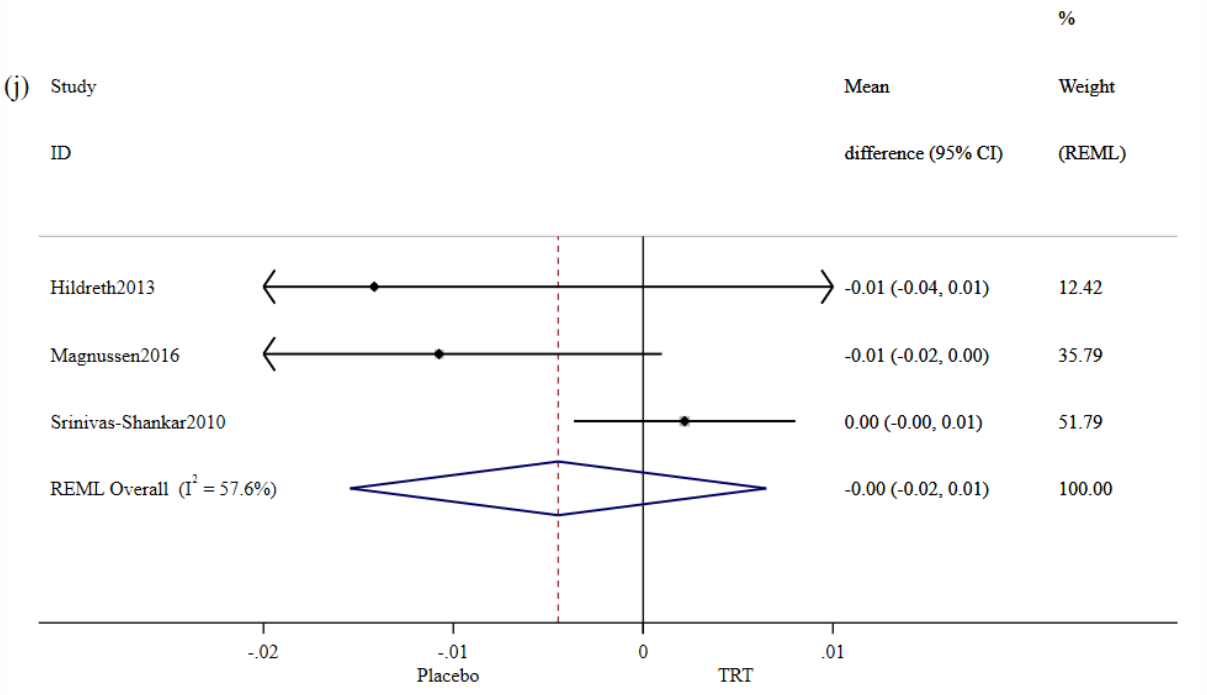
(g)


StudyID
Mean difference (95% CI)
% Weight
IPD
Amory2004 0.01 (0.00, 0.02) 33.48
Hildreth2013 0.00 (-0.01, 0.01) 29.99
Magnussen2016 -0.00 (-0.01, 0.01) 32.88
Subtotal (I-squared = 67.7%, p = 0.045) 0.00 (-0.01, 0.01) 96.36
Aggregate data
Kenny2010 0.01 (-0.04, 0.06) 3.64
Subtotal (I-squared = .%, p = .) 0.01 (-0.04, 0.06) 3.64
Overall (I-squared = 52.0%, p = 0.100) 0.00 (-0.01, 0.01) 100.00
-.06
0
.02
.04
.06
Placebo
TRT

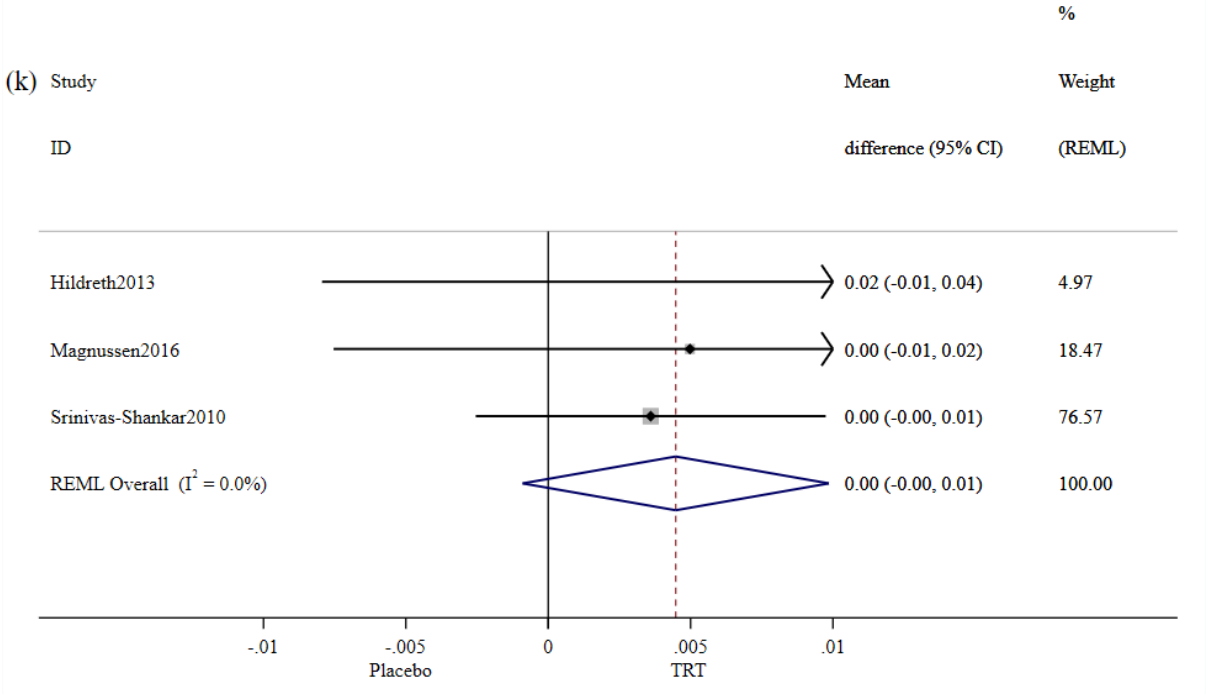

(h)
Study
ID
Mean
difference (95% CI)
%
Weight
(REML)
Amory2004
0.01 (-0.00, 0.03)
100.00
Magnussen2016
1.81 (-1.73, 5.34)
0.00
REML Overall (I² = 0.0%)
0.01 (-0.00, 0.03)
100.00
-.04
-.03
-.02
-.01
0
.01
.02
.03
.04
Placebo
TRT


(i)
Study
ID
Mean
difference (95% CI)
%
Weight
(REML)
Hildreth2013
0.01 (-0.01, 0.03)
22.68
Srinivas-Shankar2010
0.01 (-0.00, 0.02)
77.32
REML Overall (I² = 0.0%)
0.01 (-0.00, 0.02)
100.00
-.04
-.02
0
.02
.04
Placebo
TRT

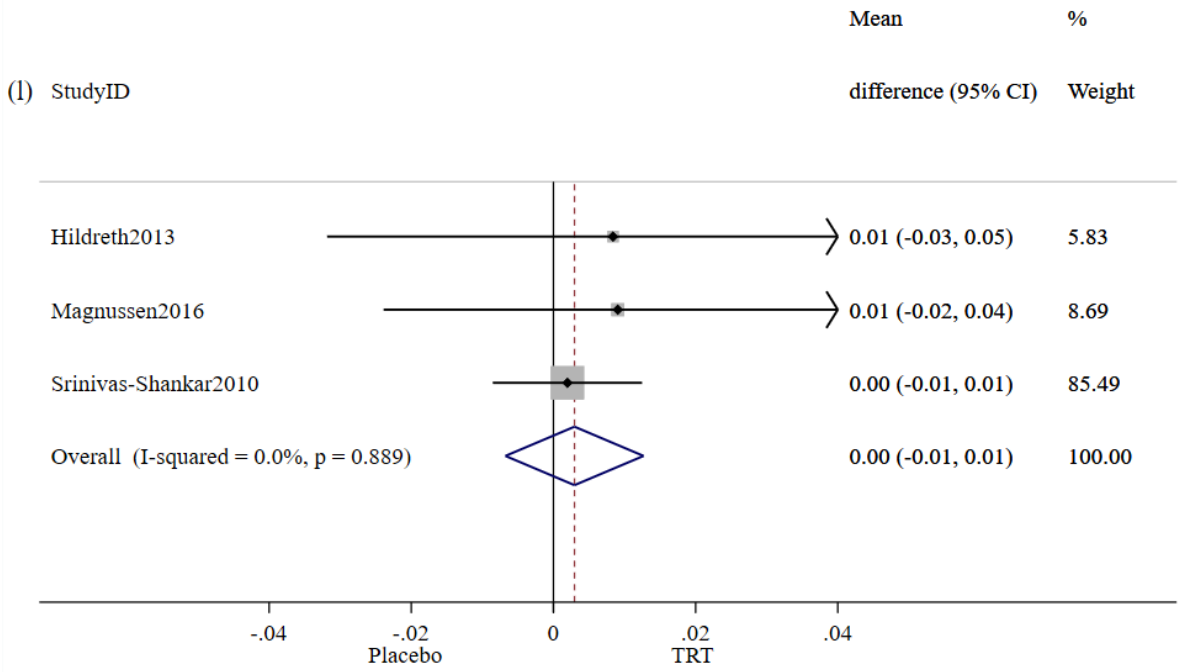
(j)


Study
ID
Mean
difference (95% CI)
%
Weight
(REML)
Hildreth2013
-0.01 (-0.04, 0.01)
12.42
Magnussen2016
-0.01 (-0.02, 0.00)
35.79
Srinivas-Shankar2010
0.00 (-0.00, 0.01)
51.79
REML Overall (I² = 57.6%)
-0.00 (-0.02, 0.01)
100.00
-.02
-.01
0
.01
Placebo
TRT

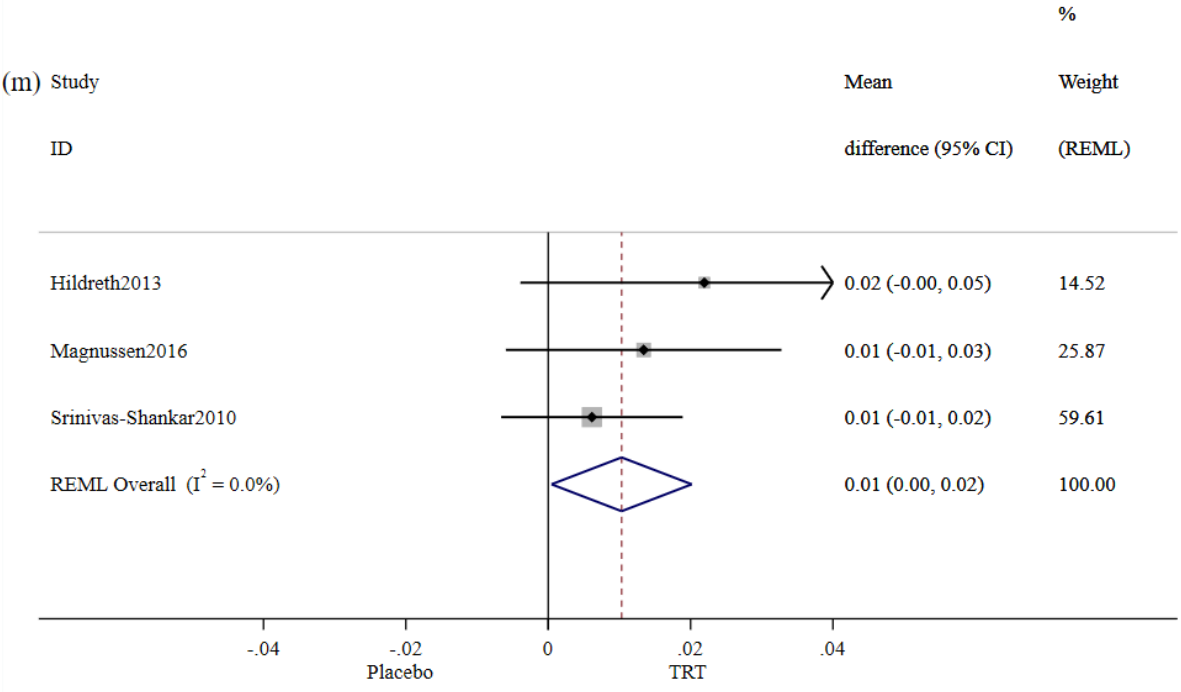
(k)

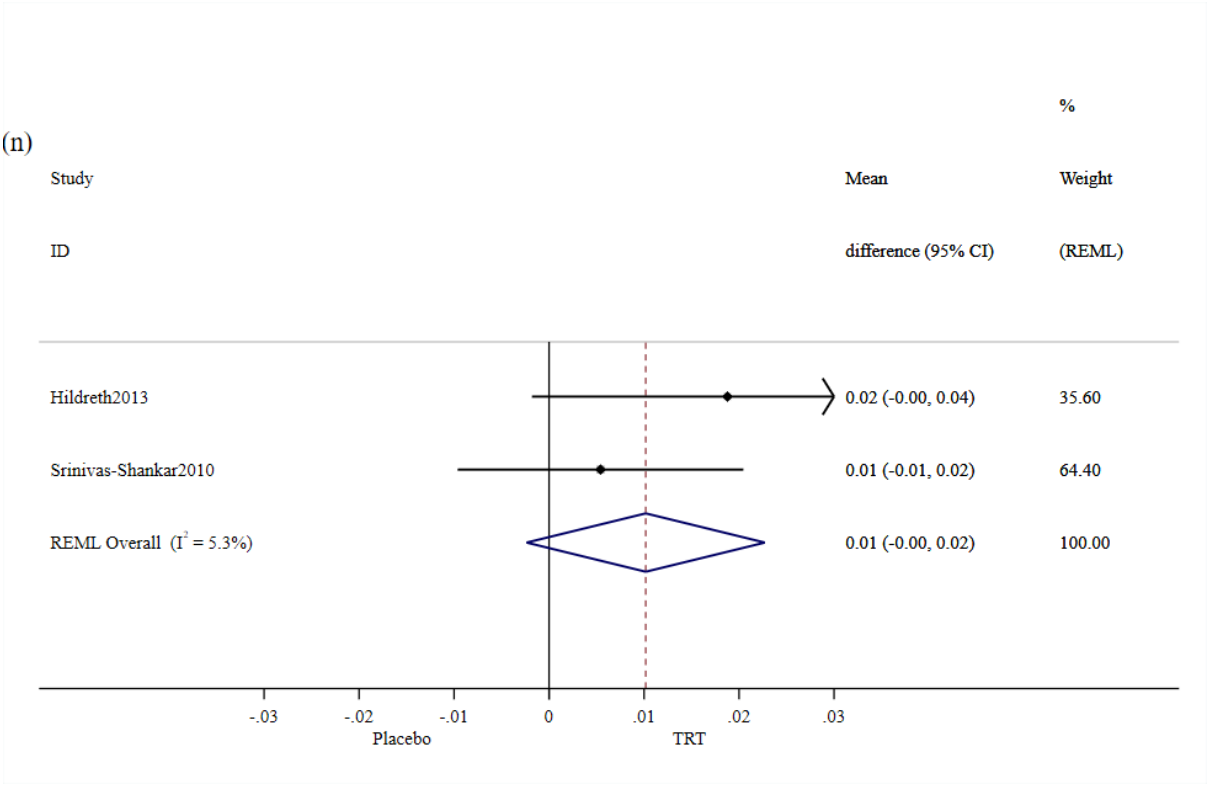

Study
ID
Mean
difference (95% CI)
%
Weight
(REML)
Hildreth2013
0.02 (-0.01, 0.04)
4.97
Magnussen2016
0.00 (-0.01, 0.02)
18.47
Srinivas-Shankar2010
0.00 (-0.00, 0.01)
76.57
REML Overall (I² = 0.0%)
0.00 (-0.00, 0.01)
100.00
-.01
-.005
0
.005
.01
Placebo
TRT

(l)


StudyID
Mean difference (95% CI)
%
Weight
Hildreth2013
0.01 (-0.03, 0.05)
5.83
Magnussen2016
0.01 (-0.02, 0.04)
8.69
Srinivas-Shankar2010
0.00 (-0.01, 0.01)
85.49
Overall (I-squared = 0.0%, p = 0.889)
0.00 (-0.01, 0.01)
100.00
-.04
-.02
0
.02
.04
Placebo
TRT

(m)


Study ID
Mean difference (95% CI)
%
Weight (REML)
Hildreth2013
0.02 (-0.00, 0.05)
14.52
Magnussen2016
0.01 (-0.01, 0.03)
25.87
Srinivas-Shankar2010
0.01 (-0.01, 0.02)
59.61
REML Overall ($I^2$ = 0.0%)
0.01 (0.00, 0.02)
100.00
-.04
-.02
0
.02
.04
Placebo
TRT



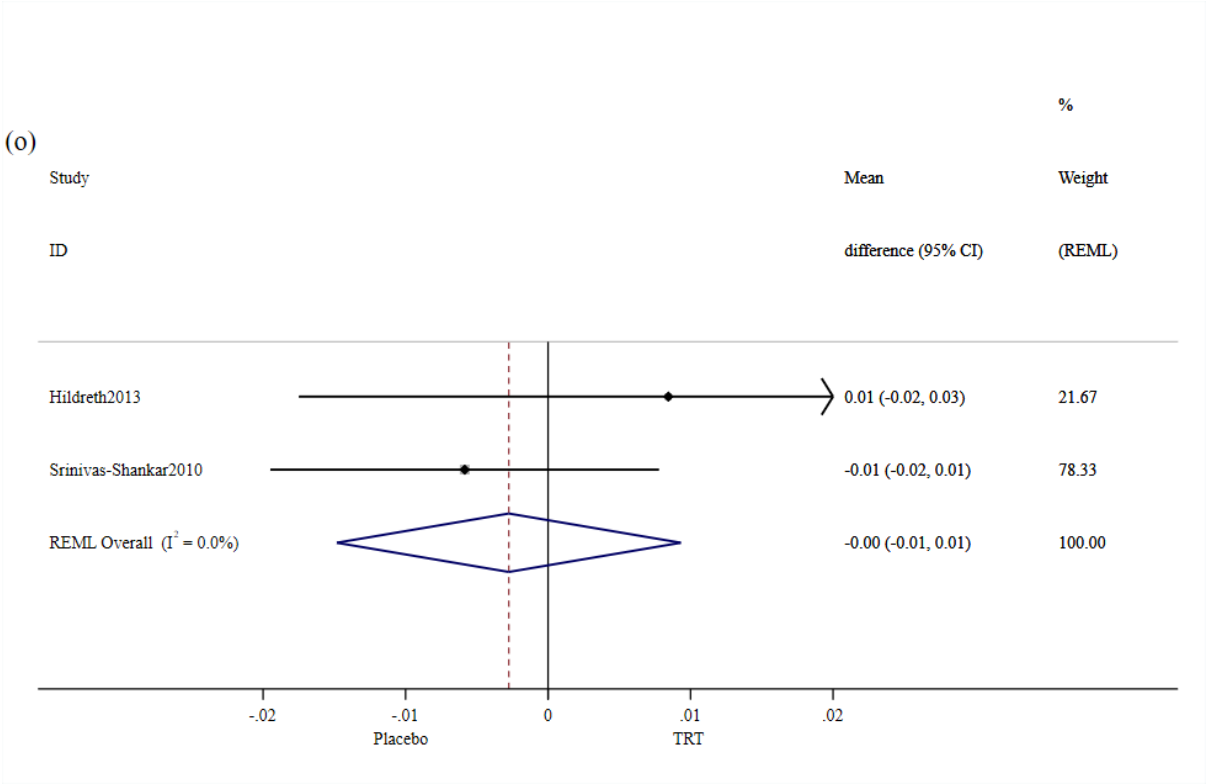




**Figure 13. Two-stage meta-analysis for increase in bone mineral density (g/cm$^2$): (a) total score; (b) Sub-total; (c) Femoral neck; (d) Lumbar spine; (e) Thoracic spine; (f) Total hip; (g) Trochanter; (h) Intertrochanter; (i) Pelvis; (j) Left arm; (k) Right arm; (l) Left leg; (m) Right leg; (n) Left rib; (o) Right rib.**

CI Confidence Interval; TRT Testosterone Replacement Therapy; REML Restricted Maximum Likelihood.
*Data presented as change from baseline.

## References


1. Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, et al. Exogenous Testosterone or Testosterone with Finasteride Increases Bone Mineral Density in Older Men with Low Serum Testosterone. J Clin Endocrinol Metab. 2004;**89**(2):503-10.

2. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, et al. Adverse events associated with testosterone administration. N Engl J Med. 2010;**363**(2):109-22.

3. Basaria S, Harman SM, Travison TG, Hodis H, Tsitouras P, Budoff M, et al. Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial. JAMA. 2015;**314**(6):570-81.

4. Brock G, Heiselman D, Maggi M, Kim SW, Rodríguez Vallejo JM, Behre HM, et al. Effect of Testosterone Solution 2% on Testosterone Concentration, Sex Drive and Energy in Hypogonadal Men: Results of a Placebo Controlled Study. J Urol. 2016;**195**(3):699-705.

5. Emmelot-Vonk MH, Verhaar HJJ, Pour HRN, Aleman A, Lock T, Bosch J, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men - A randomized controlled trial. JAMA. 2008;**299**(1):39-52.

6. Gianatti EJ, Dupuis P, Hoermann R, Zajac JD, Grossmann M. Effect of testosterone treatment on constitutional and sexual symptoms in men with type 2 diabetes in a randomized, placebo-controlled clinical trial. J Clin Endocrinol Metab. 2014;**99**(10):3821-8.

7. Giltay EJ, Tishova YA, Mskhalaya GJ, Gooren LJ, Saad F, Kalinchenko SY. Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. J Sex Med. 2010;**7**(7):2572-82.

8. Groti K, Žuran I, Antonič B, Foršnarič L, Pfeifer M. The impact of testosterone replacement therapy on glycemic control, vascular function, and components of the metabolic syndrome in obese hypogonadal men with type 2 diabetes. Aging Male. 2018;**21**(3):158-69.

9. Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P, et al. The response to testosterone undecanoate in men with type 2 diabetes is dependent on achieving threshold serum levels (the BLAST study). Int J Clin Pract. 2014;**68**(2):203-15.

10. Hildreth KL, Barry DW, Moreau KL, Vande Griend J, Meacham RB, Nakamura T, et al. Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. J Clin Endocrinol Metab. 2013;**98**(5):1891-900.

11. Ho CC, Tong SF, Low WY, Ng CJ, Khoo EM, Lee VK, et al. A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale. BJU Int. 2012;**110**(2):260-5.

12. Magnussen LV, Glintborg D, Hermann P, Hougaard DM, Højlund K, Andersen M. Effect of testosterone on insulin sensitivity, oxidative metabolism and body composition in aging men with type 2 diabetes on metformin monotherapy. Diabetes Obes Metab. 2016;**18**(10):980-9.

13. Marks LS, Mazer NA, Mostaghel E, Hess DL, Dorey FJ, Epstein JI, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism - A randomized controlled trial. JAMA. 2006;**296**(19):2351-61.

14. Merza Z, Blumsohn A, Mah PM, Meads DM, McKenna SP, Wylie K, et al. Double-blind placebo-controlled study of testosterone patch therapy on bone turnover in men with borderline hypogonadism. Int J Androl. 2006;**29**(3):381-91.

15. Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Effects of Testosterone Treatment in Older Men. N Engl J Med. 2016;**374**(7):611-24.

16. Srinivas-Shankar U, Roberts SA, Connolly MJ, O'Connell MD, Adams JE, Oldham JA, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2010;**95**(2):639-50.

17. Svartberg J, Agledahl I, Figenschau Y, Sildnes T, Waterloo K, Jorde R. Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. Int J Impot Res. 2008;**20**(4):378-87.

18. Aversa A, Bruzziches R, Francomano D, Rosano G, Isidori AM, Lenzi A, et al. [a] Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. J Sex Med. 2010;**7**(10):3495-503.

19. Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A. [b] Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. J Endocrinol Invest. 2010;**33**(11):776-83.

20. Basurto L, Zarate A, Gomez R, Vargas C, Saucedo R, Galvan R. Effect of testosterone therapy on lumbar spine and hip mineral density in elderly men. Aging Male. 2008;**11**(3):140-5.

21. Behre HM, Tammela TL, Arver S, Tolrá JR, Bonifacio V, Lamche M, et al. A randomized, double-blind, placebo-controlled trial of testosterone gel on body composition and health-related quality-of-life in men with hypogonadal to low-normal levels of serum testosterone and symptoms of androgen deficiency over 6 months with 12 months open-label follow-up. Aging Male. 2012;**15**(4):198-207.

22. Borst SE, Yarrow JF, Conover CF, Nseyo U, Meuleman JR, Lipinska JA, et al. Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. Am J Physiol Endocrinol Metab. 2014;**306**(4):E433-42.

23. Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. Urol. 2004;**63**(4):641-6.

24. Cherrier MM, Anderson K, Shofer J, Millard S, Matsumoto AM. Testosterone treatment of men with mild cognitive impairment and low testosterone levels. Am J Alzheimers Dis Other Demen. 2015;**30**(4):421-30.

25. Chiang HS, Hwang TI, Hsui YS, Lin YC, Chen HE, Chen GC, et al. Transdermal testosterone gel increases serum testosterone levels in hypogonadal men in Taiwan with improvements in sexual function. Int J Impot Res. 2007;**19**(4):411-7.

26. Clague JE, Wu FC, Horan MA. Difficulties in measuring the effect of testosterone replacement therapy on muscle function in older men. Int J Androl. 1999;**22**(4):261-5.

27. Dhindsa S, Ghanim H, Batra M, Kuhadiya ND, Abuaysheh S, Sandhu S, et al. Insulin Resistance and Inflammation in Hypogonadotropic Hypogonadism and Their Reduction After Testosterone Replacement in Men With Type 2 Diabetes. Diabetes Care. 2016;**39**(1):82-91.

28. Dias JP, Melvin D, Simonsick EM, Carlson O, Shardell MD, Ferrucci L, et al. Effects of aromatase inhibition vs. testosterone in older men with low testosterone: randomized-controlled trial. Andrology. 2016;**4**(1):33-40.

29. Jones TH, Arver S, Behre HM, Buvat J, Meuleman E, Moncada I, et al. Testosterone Replacement in Hypogonadal Men With Type 2 Diabetes and/or Metabolic Syndrome (the TIMES2 Study). Diabetes Care. 2011;**34**(4):828-37.

30. Kaufman JM, Miller MG, Garwin JL, Fitzpatrick S, McWhirter C, Brennan JJ. Efficacy and safety study of 1.62% testosterone gel for the treatment of hypogonadal men. J Sex Med. 2011;**8**(7):2079-89.

31. Kenny AM, Kleppinger A, Annis K, Rathier M, Browner B, Judge JO, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. J Am Geriatr Soc. 2010;**58**(6):1134-43.

32. Morales A, Black A, Emerson L, Barkin J, Kuzmarov I, Day A. Androgens and sexual function: a placebo-controlled, randomized, double-blind study of testosterone vs. dehydroepiandrosterone in men with sexual dysfunction and androgen deficiency. Aging Male. 2009;**12**(4):104-12.

33. Paduch DA, Polzer PK, Ni X, Basaria S. Testosterone Replacement in Androgen-Deficient Men With Ejaculatory Dysfunction: A Randomized Controlled Trial. J Clin Endocrinol Metab. 2015;**100**(8):2956-62.

34. Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand R. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. J Clin Endocrinol Metab. 2003;**88**(6):2673-81.

35. Wang YJ, Zhan JK, Huang W, Wang Y, Liu Y, Wang S, et al. Effects of low-dose testosterone undecanoate treatment on bone mineral density and bone turnover markers in elderly male osteoporosis with low serum testosterone. Int J Endocrinol. 2013;**2013**:570413.